

PERCUTANEOUS ABSORPTION PREPARATIONS

*This application is a 371 of PCT/JP00/05525 filed August 18, 2000.*  
TECHNICAL FIELD

The present invention relates to percutaneous  
5 absorption preparations which make it possible to  
continuously absorb compounds having a melatonin receptor  
agonism into a patient's body via a skin (contact surface)  
with high efficiency only during a patient's sleep  
(absorption decreases before the patient wakes up), and  
10 hence are effective for control of a biological rhythm,  
typically sleep-awake rhythm which leads a natural sleep,  
control of jet lag and preventive and therapeutic  
treatments of, for example, somnipathy.

15 BACKGROUND ART

Compounds having a melatonin  $ML_1$  receptor agonist  
activity bind to a melatonin  $ML_1$  receptor on a cell  
membrane and express a melatonin-like action. A diurnal  
variation of melatonin is such that its blood concentration  
20 increases from about 8 o'clock at night, reaches the  
maximum concentration from about 12 o'clock to 2 o'clock in  
the middle of night and decreases to the initial level  
until about 8 o'clock in the morning. This diurnal  
variation decreases in accordance with aging, which is  
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the like.

On the other hand, as for percutaneous absorption preparations of melatonin receptor agonist, Japanese Unexamined Patent Publications JP A 6-72874, JP A 10-182455, 5 JP A 10-29934 and JP A 10-29933 have been currently reported.

It is important for a patient of somnipathy that the blood concentration of melatonin peaks at 4 to 6 hours after going to bed, and hence it is also necessary for the 10 case of the melatonin  $ML_1$  receptor agonist to control the blood concentration so as to compensate the melatonin pattern in healthy condition. The conventional percutaneous absorption preparations of melatonin receptor agonist, however, are not satisfactory as medication for 15 preventing or treating somnipathy or the like because its absorption efficiency is not high enough and hence it cannot provide a one-peak blood concentration passage characteristic in which the blood concentration rapidly increases after affixing before going to bed and levels off 20 at an effective blood concentration during sleep and has decreases to an acceptable level by the time of wake-up.

The present invention provides convenient percutaneous absorption preparations of compounds having a melatonin  $ML_1$  receptor agonist activity, that is, percutaneous absorption 25 preparations of while-asleep-application (night affix) type

for leading a normal sleep, which makes it possible that the compounds are absorbed in percutaneous manner with high efficiency during a sleep and show a melatonin-like effective blood-drug-concentration-time profile in which the blood concentration has decreased before the wakeup time in the morning and the action of the drug no longer continues at the time of wakeup.

#### DISCLOSURE OF THE INVENTION

As a result of enthusiastic researches on natural sleep, the inventors of the present invention have found that percutaneous absorption preparations inventively containing a compound having a melatonin receptor agonist activity and one or more members selected from fatty acid esters, polyhydric alcohol and nonionic surfactants can unexpectedly penetrate the skin at a desirable speed, exhibit a blood-drug-concentration-time profile in which the blood concentration rapidly increases after administration and the effective blood concentration is kept for 6 to 12 hours in contrast to the case where the compound is orally administered, can lead a natural sleep, and hence are useful as medications for preventing or treating jet lag, somnipathy and the like as well as medications for adjusting biological rhythm.

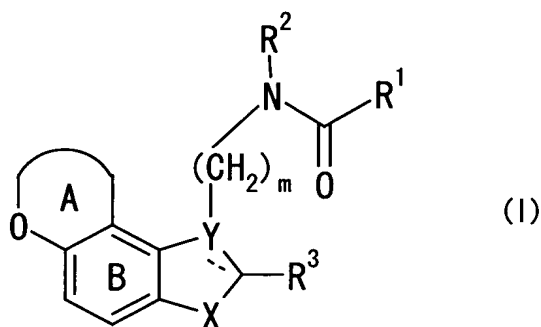
That is, the present invention provides:

(1) A percutaneous absorption preparation containing a compound having a melatonin receptor agonist activity, and one or more members selected from fatty acid esters, polyhydric alcohols and nonionic surfactants;

5 (2) The percutaneous absorption preparation according to the above-mentioned (1) containing a compound having a melatonin receptor agonist activity, and a fatty acid ester, a polyhydric alcohol and a nonionic surfactant;

10 (3) The percutaneous absorption preparation according to the above-mentioned (2), wherein the compound having a melatonin receptor agonist activity is a compound having a melatonin ML<sub>1</sub> receptor agonist activity;

15 (4) The percutaneous absorption preparation according to the above-mentioned (1), wherein the compound having a melatonin receptor agonist activity is a compound represented by the formula:



wherein, R<sup>1</sup> represents an optionally substituted hydrocarbon group, an optionally substituted amino group or  
20 an optionally substituted heterocyclic group;

$R^2$  represents a hydrogen atom or an optionally substituted hydrocarbon group;

$R^3$  represents a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted  
5 heterocyclic group;

X represents  $CHR^4$ ,  $NR^4$ , O or S in which  $R^4$  represents a hydrogen atom or an optionally substituted hydrocarbon group;

Y represents C, CH or N, provided that when X is  $CH_2$ ,  
10 Y is C or CH;

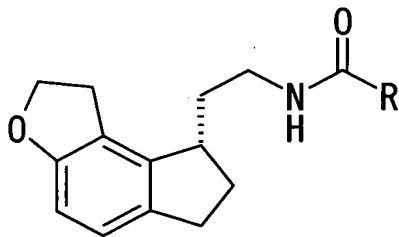
— represents a single bond or a double bond;

ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;

ring B represents an optionally substituted benzene  
15 ring; and

m represents an integer of 1 to 4;  
or a salt thereof;

(5) The percutaneous absorption preparation according to the above-mentioned (1), wherein the compound having a  
20 melatonin receptor agonist activity is a compound represented by the formula:



wherein, R represents a C<sub>1-6</sub> alkyl group;

(6) The percutaneous absorption preparation according to the above-mentioned (1), wherein the compound having a melatonin receptor agonist activity is (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide;

(7) The percutaneous absorption preparation according to the above-mentioned (1), wherein the compound having a melatonin receptor agonist activity is (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide;

(8) The percutaneous absorption preparation according to the above-mentioned (1), wherein the fatty acid ester is an ester of a carboxylic acid having 6 to 22 carbon atoms and an alkyl alcohol having 1 to 12 carbon atoms;

(9) The percutaneous absorption preparation according to the above-mentioned (1), wherein the fatty acid ester is isopropyl myristate, isopropyl palmitate, butyl myristate, or diethyl sebacate;

(10) The percutaneous absorption preparation according to the above-mentioned (1), wherein the fatty acid ester is isopropyl myristate;

(11) The percutaneous absorption preparation according to the above-mentioned (1), wherein the polyhydric alcohol is ethylene glycol, propylene glycol, 1,3-butylene glycol, glycerin or polyethylene glycol;

(12) The percutaneous absorption preparation according

to the above-mentioned (1), wherein the polyhydric alcohol is propylene glycol;

(13) The percutaneous absorption preparation according to the above-mentioned (1), wherein the polyhydric alcohol  
5 is polyethylene glycol;

(14) The percutaneous absorption preparation according to the above-mentioned (1), wherein the polyhydric alcohol is polyethylene glycol having a molecular weight of about 200 to about 1000;

10 (15) The percutaneous absorption preparation according to (1), wherein the nonionic surfactant is a fatty acid amide, a polyhydric alcohol fatty acid ester or a polyglycerol fatty acid ester;

(16) The percutaneous absorption preparation according  
15 to the above-mentioned (1), wherein the nonionic surfactant is a fatty acid amide;

(17) The percutaneous absorption preparation according to the above-mentioned (16), wherein the fatty acid amide is lauric diethanolamide or a compound including the same;

20 (18) The percutaneous absorption preparation according to the above-mentioned (16), wherein the fatty acid amide is coconut fatty acid diethanol amide;

(19) The percutaneous absorption preparation according to the above-mentioned (1) containing (S)-N-[2-(1,6,7,8-  
25 tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,



isopropyl myristate, polyethylene glycol and lauric diethanol amide;

(20) The percutaneous absorption preparation according to the above-mentioned (1) containing (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide,  
5 isopropyl myristate, polyethylene glycol and lauric diethanol amide;

(21) The percutaneous absorption preparation according to the above-mentioned (1) which is a skin plaster;

10 (22) The percutaneous absorption preparation according to the above-mentioned (1) containing in a skin contact member, a compound having a melatonin receptor agonist activity and one or more members selected from fatty acid esters, polyhydric alcohols and nonionic surfactants;

15 (23) The percutaneous absorption preparation according to the above-mentioned (22) containing in a skin contact member, a compound having a melatonin receptor agonist activity, and a fatty acid ester, a polyhydric alcohol and a nonionic surfactant;

20 (24) The percutaneous absorption preparation according to the above-mentioned (22) containing in a skin contact member, an about 1 to about 30% by weight of fatty acid ester with respect to a weight of the skin contact member;

(25) The percutaneous absorption preparation according  
25 to the above-mentioned (22) containing in a skin contact

member, an about 1 to about 30% by weight of polyhydric alcohol with respect to a weight of the skin contact member;

5 (26) The percutaneous absorption preparation according to the above-mentioned (22) containing in a skin contact member, an about 1 to about 15% by weight of nonionic surfactant with respect to a weight of the skin contact member;

10 (27) The percutaneous absorption preparation according to the above-mentioned (22) containing in a skin contact member, an adhesive agent;

(28) The percutaneous absorption preparation according to the above-mentioned (22), wherein the adhesive agent is an acrylic adhesive agent;

15 (29) The percutaneous absorption preparation according to the above-mentioned (22) containing in a skin contact member, an about 0.01 to about 70% by weight of compound having a melatonin receptor agonist activity with respect to a weight of the skin contact member;

20 (30) The percutaneous absorption preparation according to the above-mentioned (22) containing in a skin contact member, an about 5 to about 99% by weight of adhesive agent with respect to a weight of the skin contact member;

(31) The percutaneous absorption preparation according to the above-mentioned (22), wherein a content of the

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compound having a melatonin receptor agonist activity per unit skin contact surface of a skin contact member is about 0.01 to about 100 mg/cm<sup>2</sup>;

(32) The percutaneous absorption preparation according to the above-mentioned (22) containing in a skin contact member, a filler;

(33) The percutaneous absorption preparation according to the above-mentioned (32), wherein the filler is silicon dioxide;

(34) The percutaneous absorption preparation according to the above-mentioned (1) which is to be affixed between about 6 hours before bedtime to just before bedtime;

(35) The percutaneous absorption preparation according to the above-mentioned (1) which maintains an effective concentration of the compound having a melatonin receptor agonist activity in blood for about 6 hours to about 12 hours;

(36) The percutaneous absorption preparation according to the above-mentioned (1) which maintains an effective concentration of the compound having a melatonin receptor agonist activity in blood until about 1 to about 2 hours before waking up;

(37) The percutaneous absorption preparation according to the above-mentioned (1), wherein an effective blood concentration of the compound having a melatonin receptor

agonist activity exhibits a one peak pattern within 12 hours after administration;

(38) The percutaneous absorption preparation according to the above-mentioned (37), wherein a peak of the effective blood concentration of the compound having a melatonin receptor agonist activity appears within about 10 hours after administration;

(39) A preventive and therapeutic method of diseases related to melatonin, characterized by administering a percutaneous absorption preparation which contains a compound having a melatonin receptor agonist activity, and one or more members selected from fatty acid esters, polyhydric alcohols and nonionic surfactants;

(40) A percutaneous absorption method of a compound having a melatonin receptor agonist activity, wherein the percutaneous absorption preparation contains a compound having a melatonin receptor agonist activity and one or more members selected from fatty acid esters, polyhydric alcohols and nonionic surfactants; and

(41) A use of one or more members selected from fatty acid esters, polyhydric alcohols and nonionic surfactants for achieving percutaneous absorption of a compound having a melatonin receptor agonist activity.

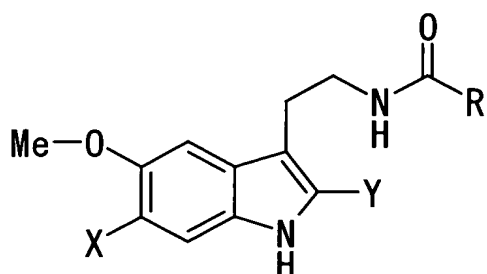
The percutaneous absorption preparations according to the present invention can be applied to any compounds

having a melatonin receptor (ML<sub>1</sub>, ML<sub>2</sub>, nuclear receptor, etc.) agonist activity, and among them, can preferably applied to compounds having a melatonin ML<sub>1</sub> receptor agonist activity.

5           The term "melatonin ML<sub>1</sub> receptor agonist activity" used in the present invention means an action of specifically binding to a melatonin ML<sub>1</sub> receptor which is one of the melatonin receptors on a cell membrane and proving a comparative or better effect than the case where  
10   the receptor binds to melatonin. As a result of binding to the melatonin ML<sub>1</sub> receptor, a sleep inducing action is derived, and this action induces a sleep which is similar to a natural sleep and causes no discomfort on the next day in contrast to the sleep action by diazepam or the like.  
15   Therefore, compounds having a melatonin ML<sub>1</sub> receptor agonist activity can be applied for adjustment of biological rhythms, typically sleep-awake rhythm, adjustment of a jet lag, treatment of a somnipathy and the like.

20           There is no particular limitation for the compounds having a melatonin ML<sub>1</sub> receptor agonist activity insofar as they have an equivalent action, and examples of melatonin agonists or antagonists thereof include:

(1) Compounds represented by the formula disclosed in  
25   EP-A-578620:



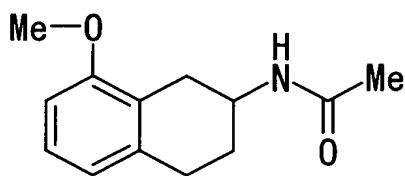
X=H, Y=Br, R=Me

X=H, Y=I, R=Me

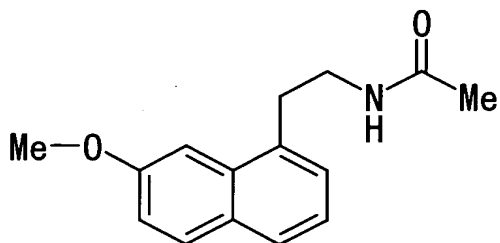
X=Cl, Y=H, R=Me

X=H, Y=CH<sub>3</sub>, R=cyclopropyl

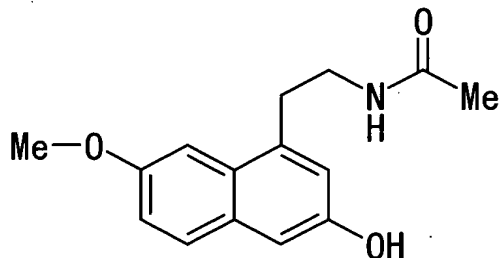
(2) Compounds represented by the formula disclosed in  
USP 411675:



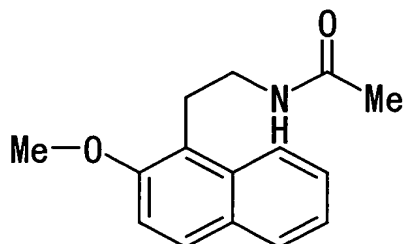
5 (3) Compounds represented by the formula disclosed in  
Japanese Unexamined Patent Publication JP-A 7-048331 (EP-A-  
447285):



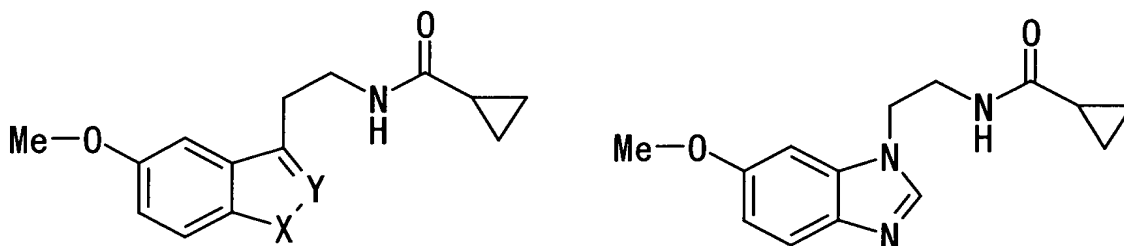
10 (4) Compounds represented by the formula disclosed in  
FR-014630:



(5) Compounds represented by the formula disclosed in  
EP-A-591057:

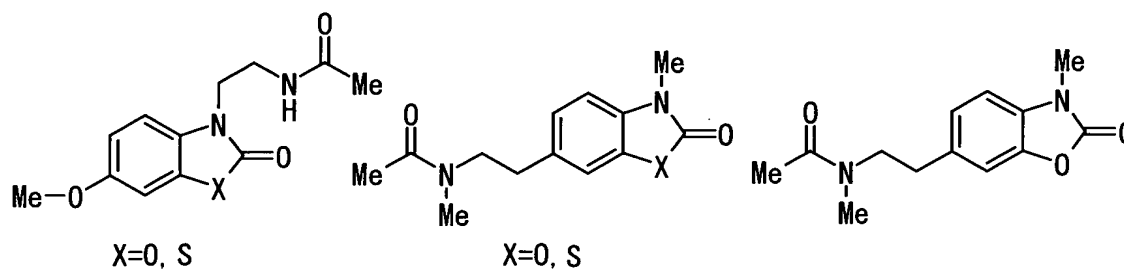


(6) Compounds represented by the formulae disclosed in  
5 EP-A-527687:



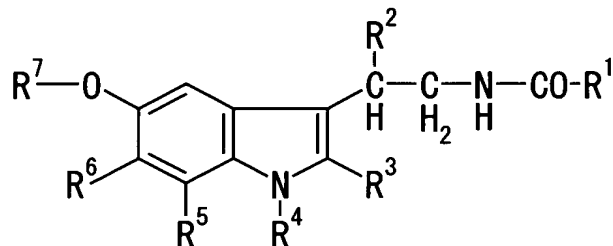
X=S, O, Y=CH  
X=O, NH, Y=N

(7) Compounds represented by the formulae disclosed in  
EP-A-506539:



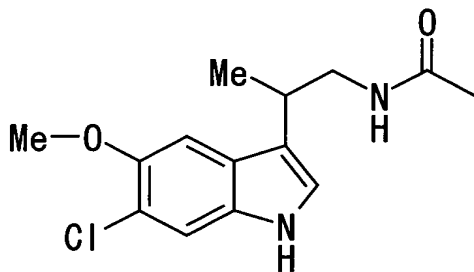
10 (8) Compounds represented by the formula disclosed in  
Japanese Unexamined Patent Publication JP-A 7-196493 or JP-

A 63-196563:



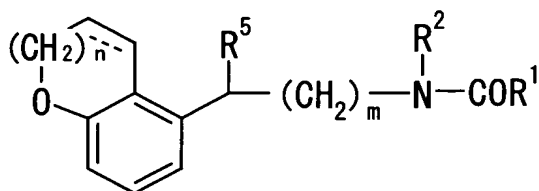
wherein  $R^1$  represents hydrogen,  $C_1-C_4$  alkyl or  $C_1-C_4$  alkoxy;  
 $R^2$  represents a hydrogen or  $C_1-C_4$  alkyl;  $R^3$  represents  
 5 hydrogen,  $C_1-C_4$  alkyl, phenyl or substituted phenyl;  $R^4$   
 represents hydrogen, haloacetyl,  $C_1-C_5$  alkanoyl, benzoyl,  
 or halo- or methyl-substituted benzoyl;  $R^5$  and  $R^6$  represent,  
 independently, a hydrogen or halo; and  $R^7$  represents a  
 hydrogen or  $C_1-C_4$  alkyl; provided that when each of  $R^3$ ,  $R^4$   
 10 and  $R^5$  is hydrogen,  $R^2$  is  $C_1-C_4$  alkyl);

or salts thereof, among these the compounds represented by  
 the formula (LY156735):



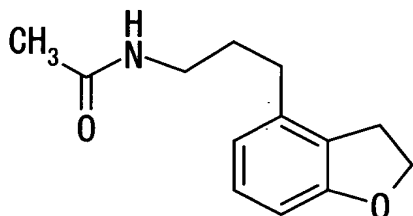
(9) Compounds represented by the formula disclosed in



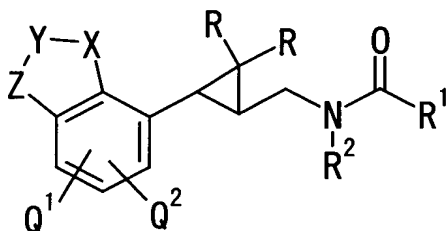


wherein  $R^1$  and  $R^2$  are the same or different and each represents hydrogen,  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl or aryl;  $R^3$  and  $R^4$  are the same or different and each represents  
 5 hydrogen, a halogen,  $C_{1-6}$  alkyl or substituted aryl;  $R^5$  represents a hydrogen or  $C_{1-6}$  alkyl;  $n$  represents 0, 1 or 2; and  $m$  represents 1, 2, 3 or 4;

----- represents a single bond or a double bond;  
 and salts thereof, and among these the compounds  
 10 represented by the formula:



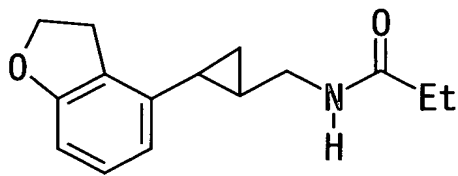
(10) Compounds represented by the formula disclosed in  
 WO 98/25606:



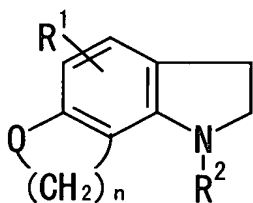
15 wherein  $Q^1$  and  $Q^2$  each represents a hydrogen or a halogen;  $X$  represents  $CH_2$ ,  $CH$  or an oxygen;  $Y$  represent  $CR^3$ ,  $CR^3R^4$  or

$(CH_2)_n$  ( $n=1-4$ ); Z represents  $CH_2$ , CH or an oxygen; R represents hydrogen, a halogen or  $C_{1-4}$  alkyl; m represents 1 or 2;  $R^1$  represents  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{1-3}$  haloalkyl,  $C_{1-6}$  alkylamino,  $C_{2-6}$  alkenyl,  $C_{1-4}$  alkoxy( $C_{1-4}$ )alkyl,  $C_{1-4}$  alkylthio( $C_{1-4}$ )alkyl or trifluoromethylalkyl;  $R^2$  is a hydrogen or  $C_{1-4}$  alkyl; and  $R^3$  and  $R^4$  each represents a hydrogen or  $C_{1-4}$  alkyl;

or salts thereof, and among these the compounds represented by the formula:



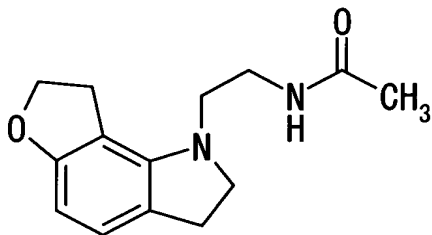
(11) Compounds represented by the formula disclosed in Japanese Examined Patent Publication JP-B2 9-507057:



wherein  $R^1$  represents hydrogen, a halogen or  $C_{1-6}$  alkyl;  $R^2$  represents  $-CR^3R^4(CH_2)_pNR^5COR^6$ ;  $R^3$ ,  $R^4$  and  $R^5$  may be the same or different and each represents a hydrogen or  $C_{1-6}$  alkyl;  $R^6$  represents  $C_{1-6}$  alkyl or  $C_{3-7}$  cycloalkyl; n represents an integer of 2, 3 or 4; and p represents an integer of 1, 2, 3 or 4);

and salts thereof, and among these the compounds

represented by the formula:



,and the compound (I) are used. Among these, the compound (I) which represents a high affinity for a melatonin  
5 receptor and a particularly high selectivity for the ML<sub>1</sub> receptor is preferred.

The "hydrocarbon group" in "optionally substituted hydrocarbon group" as referred to herein includes, for example, an aliphatic hydrocarbon group, a mono-cyclic  
10 saturated hydrocarbon group, an aromatic hydrocarbon group, etc.,

and this preferably has from 1 to 16 carbon atoms. Concretely, this includes, for example, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an  
15 aryl group, etc.

The "alkyl group" is, for example, preferably a lower alkyl group and generally includes C<sub>1-6</sub> alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

20 The "alkenyl group" is, for example, preferably a lower alkenyl group and generally includes C<sub>2-6</sub> alkenyl groups such as vinyl, 1-propenyl, allyl, isopropenyl,

butenyl, isobutenyl, etc.

The "alkynyl group" is, for example, preferably a lower alkynyl group and generally includes  $C_{2-6}$  alkynyl groups such as ethynyl, propargyl, 1-propynyl, etc.

5        The "cycloalkyl group" is, for example, preferably a lower cycloalkyl group and generally includes  $C_{3-6}$  cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

10        The "aryl group" is preferably a  $C_{6-14}$  aryl group, including, for example, phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl, etc. For example, phenyl is generally used.

15        The substituents for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" include, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a nitro group, a cyano group, a hydroxyl group, an optionally halogenated lower alkyl group (e.g., an optionally halogenated.  $C_{1-6}$  alkyl group such as methyl, chloromethyl, difluoromethyl, trichloromethyl, 20 trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 4,4,4-trifluorobutyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.), a 25 lower alkoxy group (e.g., a  $C_{1-6}$  alkoxy group such as

methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy, etc.), an amino group, a mono-lower alkylamino group (e.g., a mono-C<sub>1-6</sub> alkylamino group such as methylamino, ethylamino, etc.), a di-lower alkylamino group (e.g., a di-C<sub>1-6</sub> lower alkylamino group such as dimethylamino, diethylamino, etc.), a carboxyl group, a lower alkylcarbonyl group (e.g., a C<sub>1-6</sub> alkyl-carbonyl group such as acetyl, propionyl, etc.), a lower alkoxy carbonyl group (e.g., a C<sub>1-6</sub> alkoxy-carbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a carbamoyl group, a mono-lower alkylcarbamoyl group (e.g., a mono-C<sub>1-6</sub> alkyl-carbamoyl group such as methylcarbamoyl, ethylcarbamoyl, etc.), a di-lower alkylcarbamoyl group (e.g., a di-C<sub>1-6</sub> alkyl-carbamoyl group such as dimethylcarbamoyl, diethylcarbamoyl, etc.), an arylcarbamoyl group (e.g., a C<sub>6-10</sub> aryl-carbamoyl group such as phenylcarbamoyl, naphthylcarbamoyl, etc.), an aryl group (e.g., a C<sub>6-10</sub> aryl group such as phenyl, naphthyl, etc.), an aryloxy group (e.g., a C<sub>6-10</sub> aryloxy group such as phenyloxy, naphthyloxy, etc.), an optionally halogenated lower alkylcarbonylamino group (e.g., an optionally halogenated C<sub>1-6</sub> alkyl-carbonylamino group such as acetylamino, trifluoroacetylamino, etc.), an oxo group, etc. The "hydrocarbon group" of the "optionally substituted hydrocarbon group" may have 1 to 5, preferably 1 to 3

substituents selected from those mentioned above, at any substitutable positions in the group. When the number of the substituents is two or more, each of the substituents may be the same or different.

5       The "heterocyclic group" in "optionally substituted heterocyclic group" as referred to herein includes, for example, a 5- to 14-membered (preferably, 5- to 10-membered), mono- to tri-cyclic (preferably mono- or di-cyclic) heterocyclic group, each having 1 or 2 kinds, 1 to  
10   4 (preferably 1 to 3) hetero atoms selected from nitrogen, oxygen and sulfur, in addition to carbon atoms. Concretely, it includes, for example, a 5-membered heterocyclic group having 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, in addition to  
15   carbon atoms, such as 2- or 3-thienyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 3- or 4-pyrazolidinyl, 2-, 4-, or 5-imidazolyl, 1,2,3-triazolyl,  
20   1,2,4-triazolyl, 1H- or 2H-tetrazolyl; a 6-membered heterocyclic group having 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen atoms, in addition to carbon atoms, such as 2-, 3- or 4-pyridyl, N-oxido-2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxido-2-, 4- or 5-pyrimidinyl, thiomorpholinyl, morpholinyl, piperidino, 2-,  
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3- or 4-piperidyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, piperazinyl, triazinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxido-3- or 4-pyridazinyl; a di- or tri-cyclic condensed heterocyclic group having 1 to 4 hetero atoms

5 selected from oxygen, sulfur and nitrogen atoms, in addition to carbon atoms (preferably, a group to be formed by condensing the above-mentioned 5- or 6-membered cyclic group with one or two 5- or 6-membered cyclic groups each optionally having 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen atoms, in addition to carbon atoms),  
10 such as indolyl, benzofuryl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolyl, isoquinolyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolidinyl, quinolidinyl, 1,8-naphthyridinyl, dibenzofuranyl, carbazolyl, acridinyl,  
15 phenanthridinyl, chromanyl, phenothiazinyl, phenoxazinyl, etc. Of these, preferred are 5- to 7-membered (preferably, 5- or 6-membered) heterocyclic groups each having 1 to 3 hetero atoms selected from oxygen, sulfur and nitrogen atoms, in addition to carbon atoms.

20 The substituents for the "heterocyclic group" of the "optionally substituted heterocyclic group" include, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a lower alkyl group (e.g., a C<sub>1-6</sub> alkyl group such as methyl, ethyl, propyl, isopropyl, butyl,  
25 isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), a

cycloalkyl group (e.g., a C<sub>3-6</sub> cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), a lower alkynyl group (e.g., a C<sub>2-6</sub> alkynyl group such as ethynyl, 1-propynyl, propargyl, etc.), a lower alkenyl group (e.g., a C<sub>2-6</sub> alkenyl group such as vinyl, allyl, isopropenyl, butenyl, isobutenyl, etc.), an aralkyl group (e.g., a C<sub>7-11</sub> aralkyl group such as benzyl, .alpha.-methylbenzyl, phenethyl, etc.), an aryl group (e.g., a C<sub>6-10</sub> aryl group such as phenyl, naphthyl, etc., preferably phenyl), a lower alkoxy group (e.g., a C<sub>1-6</sub> alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.), an aryloxy group (e.g., a C<sub>6-10</sub> aryloxy group such as phenoxy, etc.), a lower alkanoyl group (e.g., formyl, a C<sub>1-6</sub> alkyl-carbonyl group such as acetyl, propionyl, butyryl, isobutyryl, etc.), an arylcarbonyl group (e.g., a C<sub>6-10</sub> aryl-carbonyl group such as benzoyl, naphthoyl, etc.), a lower alkanoyloxy group (e.g., formyloxy, a C<sub>1-6</sub> alkyl-carbonyloxy group such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.), an arylcarbonyloxy group (e.g., a C<sub>6-10</sub> aryl-carbonyloxy group such as benzoyloxy, naphthoyloxy, etc.), a carboxyl group, a lower alkoxycarbonyl group (e.g., a C<sub>1-6</sub> alkoxy-carbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, etc.), an



aralkyloxycarbonyl group (e.g., a C<sub>7-11</sub> aralkyloxycarbonyl group such as benzyloxycarbonyl, etc.), a carbamoyl group, a mono-, di- or tri-halogeno-lower alkyl group (e.g., a mono-, di- or tri-halogeno-C<sub>1-4</sub> alkyl group such as

5 chloromethyl, dichloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, etc.), an oxo group, an amidino group, an imino group, an amino group, a mono-lower alkylamino group (e.g., a mono-C<sub>1-4</sub> alkylamino group, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.),

10 a di-lower alkylamino group (e.g., a di-C<sub>1-4</sub> alkylamino group such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, methylethylamino, etc.), a 3- to 6-membered cyclic amino group optionally having 1 to 3 hetero atoms selected from oxygen, sulfur and nitrogen

15 atoms, in addition to carbon atoms and one nitrogen atom (e.g., a 3- to 6-membered cyclic amino group such as aziridinyl, azetidiny, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidyl, morpholinyl, dihydropyridyl, pyridyl, N-methylpiperazinyl,

20 N-ethylpiperazinyl, etc.), an alkylenedioxy group (e.g., a C<sub>1-3</sub> alkylenedioxy group such as methylenedioxy, ethylenedioxy, etc.), a hydroxyl group, a nitro group, a cyano group, a mercapto group, a sulfo group, a sulfinio group, a phosphono group, a sulfamoyl group, a

25 monoalkylsulfamoyl group (e.g., a mono-C<sub>1-6</sub> alkylsulfamoyl

group such as N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-butylsulfamoyl, etc.), a dialkylsulfamoyl group (e.g., a di-C<sub>1-6</sub> alkylsulfamoyl group such as N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, etc.), an alkylthio group (e.g., C<sub>1-6</sub> alkylthio group such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.), an arylthio group (e.g., a C<sub>6-10</sub> arylthio group such as phenylthio, naphthylthio, etc.), a lower alkylsulfinyl group (e.g., a C<sub>1-6</sub> alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc.), an arylsulfinyl group (e.g., a C<sub>6-10</sub> arylsulfinyl group such as phenylsulfinyl, naphthylsulfinyl, etc.), a lower alkylsulfonyl group (e.g., a C<sub>1-6</sub> alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, etc.), an arylsulfonyl group (e.g., a C<sub>6-10</sub> arylsulfonyl group such as phenylsulfonyl, naphthylsulfonyl, etc.), etc.

The "heterocyclic group" of the "optionally substituted heterocyclic group" may have 1 to 5, preferably 1 to 3 substituents selected from those mentioned above, at any substitutable positions in the group. In the case that the group has two or more substituents, these substituents may be the same or different.

The "optionally substituted amino group" as referred to herein includes amino groups each optionally having one or two substituents of, for example, the above-mentioned "optionally substituted hydrocarbon groups". Preferred substituents for the above "amino group" include, for example, an optionally substituted C<sub>1-6</sub> alkyl group and an optionally substituted C<sub>6-10</sub> aryl group. The substituents which the "C<sub>1-6</sub> alkyl group" or the "C<sub>6-10</sub> aryl group" may optionally have are, for example, the same ones as the above-mentioned "hydrocarbon group" may optionally have.

The "lower alkyl group" for "optionally substituted lower alkyl group" as referred to herein includes, for example, a C<sub>1-6</sub> alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl. The lower alkyl group may optionally have 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have.

The "lower alkoxy group" in "optionally substituted lower alkoxy group" as referred to herein includes, for example, a C<sub>1-6</sub> alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy. The lower alkoxy group may optionally have 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have.

The "optionally substituted benzene ring" as referred

to herein includes, for example, a benzene ring which may optionally have one or two substituents selected from, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), an optionally substituted hydrocarbon group, an optionally substituted amino group, an amide group (e.g., a C<sub>1-3</sub> acylamino group such as formamide, acetamide, etc.), an optionally substituted lower alkoxy group and a lower alkylenedioxy group (e.g., a C<sub>1-3</sub> alkylenedioxy group such as methylenedioxy, ethylenedioxy, etc.), at any substitutable positions in the ring.

For these "optionally substituted hydrocarbon group", "optionally substituted amino group" and "optionally substituted lower alkoxy group", the same ones as those described in detail hereinabove are referred to. In the case that these "hydrocarbon group", "amino group" and "lower alkoxy group" each have two or more substituents, these substituents may be the same or different.

The "optionally substituted benzene ring" is preferably a benzene ring optionally substituted by 1 or 2 substituents selected from a halogen atom (e.g., fluorine, chlorine, etc.), a C<sub>1-6</sub> alkyl group (e.g., methyl, ethyl, etc.) and a mono-C<sub>1-6</sub> alkylamino group.

In the above-mentioned formulae, R<sup>1</sup> represents an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted

heterocyclic group.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" represented by  $R^1$  is preferably, for example, an alkyl group (e.g., a  $C_{1-6}$  alkyl group such as methyl, ethyl, propyl, isopropyl, etc.), an alkenyl group (e.g.,  $C_{2-6}$  alkenyl group such as vinyl, etc.), an alkynyl group (e.g., a  $C_{2-6}$  alkynyl group such as ethynyl), a cycloalkyl group (e.g., a  $C_{3-6}$  cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), or an aryl group (e.g., a  $C_{6-14}$  aryl group such as phenyl, etc.), especially preferably an alkyl group (e.g., a  $C_{1-6}$  alkyl group such as methyl, etc.) or a cycloalkyl group (e.g., a  $C_{3-6}$  cyclopropyl group such as cyclopropyl, etc.). These "alkyl group", "alkenyl group", "alkynyl group", "cycloalkyl group" and "aryl group" each may have 1 to 5, preferably 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have, preferably halogen atoms such as fluorines.

Preferred substituents for the "optionally substituted amino group" represented by  $R^1$ , are one or two substituents selected from, for example, an optionally substituted lower alkyl group and an optionally substituted aryl group, more preferably one substituent of an optionally substituted lower alkyl group. The "lower alkyl group" includes, for example, a  $C_{1-6}$  alkyl group such as methyl, ethyl, propyl,

isopropyl, butyl, isobutyl, sec-butyl and tert-butyl. The "lower alkyl group" may optionally have 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have. The "aryl group" includes, for example, a C<sub>6-10</sub> aryl group such as phenyl, etc. The "aryl group" may optionally have 1 to 5, preferably 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have, preferably those selected from, for example, a halogen atom such as fluorine and chlorine and a C<sub>1-6</sub> alkoxy group such as methoxy and ethoxy. The "optionally substituted amino group" includes, for example, a phenylamino group substituted by, 1 to 3 lower alkoxy groups (e.g., C<sub>1-4</sub> alkoxy groups such as methoxy, etc.) or a monoalkylamino group substituted by one lower alkyl group (e.g., a C<sub>1-4</sub> alkyl group such as methyl, ethyl, propyl, butyl, tert-butyl, etc.)

The "heterocyclic group" of the "optionally substituted heterocyclic group" represented by R<sup>1</sup> is, for example, preferably a 5- or 6-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms in addition to carbon atoms. Concretely, it includes, for example, 1-, 2- or 3-pyrrolidinyl, 2- or 4-imidazoliny, 2-, 3- or 4-pyrazolidinyl, piperidino, 2-, 3- or 4-piperidyl, 1- or 2-piperazinyl, morpholinyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 3-furyl, pyrazinyl,

2-pyrimidinyl, 3-pyrrolyl, 3-pyridazinyl, 3-isothiazolyl and 3-isoxazolyl. Especially preferably, it is a 6-membered nitrogen-containing heterocyclic group (e.g., pyridyl, etc.).

5 Preferred substituents for the "optionally substituted heterocyclic group" represented by  $R^1$  include, for example, a halogen atom (e.g., chlorine, fluorine, etc.), a  $C_{1-6}$  alkyl group (e.g., methyl, ethyl, etc.), a  $C_{1-6}$  alkoxy group (e.g., methoxy, ethoxy, etc.) and an aralkyloxycarbonyl  
10 group (e.g., a  $C_{7-12}$  aralkyloxy-carbonyl group such as benzyloxycarbonyl, etc.).

$R^1$  is, for example, preferably (i) an optionally substituted lower alkyl group, (ii) an optionally substituted lower cycloalkyl group, (iii) an optionally  
15 substituted lower alkenyl group, (iv) an optionally substituted aryl group, (v) an optionally substituted mono- or di-lower alkylamino group, (vi) an optionally substituted arylamino group or (vii) an optionally substituted 5- or 6-membered nitrogen-containing  
20 heterocyclic group.

The "lower alkyl group" is preferably a  $C_{1-6}$  alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl. The "lower cycloalkyl group" is preferably a  $C_{3-6}$  cycloalkyl group such as cyclopropyl,  
25 cyclobutyl, cyclopentyl and cyclohexyl. The "lower alkenyl

group" is preferably a C<sub>2-6</sub> alkenyl group such as vinyl, 1-propenyl and butenyl. The "aryl group" is preferably a C<sub>6-10</sub> aryl group such as phenyl, 1-naphthyl and 2-naphthyl. The "lower alkylamino group" is preferably a mono- or di-C<sub>1-6</sub> alkylamino group such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, dimethylamino, diethylamino and methylethylamino. The "arylamino group" is preferably a C<sub>6-10</sub> arylamino group such as phenylamino. The "5- or 6-membered nitrogen-containing heterocyclic group" is, for example, preferably 2-, 3- or 4-pyridyl or the like. These groups may each optionally have 1 to 5 substituents such as those referred to the mentioned-above "hydrocarbon group" may optionally have.

More preferably, R<sup>1</sup> is (i) a C<sub>1-6</sub> alkyl group optionally substituted by 1 to 4 substituents selected from a halogen atom and a C<sub>1-6</sub> alkoxy group, (ii) a C<sub>3-6</sub> cycloalkyl group, (iii) a C<sub>2-6</sub> alkenyl group, (iv) a C<sub>6-10</sub> aryl group optionally substituted by 1 to 4 substituents selected from a C<sub>1-6</sub> alkoxy group, a nitro group, a halogeno-C<sub>1-6</sub> alkyl-carbonylamino group and a halogen atom, (v) a mono- or di-C<sub>1-6</sub> alkylamino group, (vi) a C<sub>6-10</sub> arylamino group optionally substituted by one to three C<sub>1-6</sub> alkoxy groups, or (vii) a 6-membered nitrogen-containing heterocyclic group optionally substituted by one or two C<sub>7-11</sub> aralkyloxycarbonyl groups. Even more preferably, R<sup>1</sup> is an



optionally halogenated  $C_{1-6}$  alkyl group (e.g., methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 4,4,4-trifluorobutyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.), a  $C_{3-6}$  cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) or a mono- $C_{1-6}$  alkylamino group (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, etc.) Among others,  $R^1$  is preferably an optionally halogenated  $C_{1-6}$  alkyl group or a mono- $C_{1-6}$  alkylamino group, especially an optionally halogenated  $C_{1-6}$  alkyl, in particular  $C_{1-3}$  alkyl group (e.g., methyl, ethyl, propyl, etc.).

In the above-mentioned formulae,  $R^2$  represents a hydrogen atom or an optionally substituted hydrocarbon group.

$R^2$  is preferably a hydrogen atom or an optionally substituted lower ( $C_{1-6}$ ) alkyl group, more preferably a hydrogen atom or a lower ( $C_{1-6}$ ) alkyl group, even more preferably a hydrogen atom.

In the above-mentioned formulae,  $R^3$  represents a hydrogen atom, an optionally substituted hydrocarbon group or optionally substituted heterocyclic group.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" represented by  $R^3$  is preferably, for example, an alkyl group (e.g., a  $C_{1-6}$  alkyl group such as methyl, ethyl, propyl, isopropyl, etc.), an alkenyl group (e.g., a  $C_{2-6}$  alkenyl group such as vinyl, etc.), an alkynyl group (e.g., a  $C_{2-6}$  alkynyl group such as ethynyl, etc.), a cycloalkyl group (e.g., a  $C_{3-6}$  cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) or an aryl group (e.g., a  $C_{6-14}$  aryl group such as phenyl, etc.). It is more preferably an alkyl group (e.g., a  $C_{1-6}$  alkyl group such as methyl, etc.) or an aryl group (e.g., a  $C_{6-14}$  aryl groups such as phenyl, etc.). These "alkyl group", "alkenyl group", "alkynyl group", "cycloalkyl group" and "aryl group" each may optionally have 1 to 5, preferably 1 to 3 substituents such as the same ones the mentioned-above "hydrocarbon group" may optionally have (e.g., halogen atoms such as fluorines, etc.).

The "heterocyclic group" of the "optionally substituted heterocyclic group" represented by  $R^3$  is preferably a 5- or 6-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms, in addition to carbon atoms. Concretely, it includes, for example, 1-, 2- or 3-pyrrolidinyl, 2- or 4-imidazoliny, 2-, 3- or 4-pyrazolidinyl, piperidino, 2-, 3- or 4-piperidyl, 1- or 2-piperazinyl, morpholinyl, 2- or 3-

thienyl, 2-, 3- or 4-pyridyl, 2- or 3-furyl, pyrazinyl, 2-pyrimidinyl, 3-pyrrolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, etc. More preferred is a 6-membered nitrogen-containing heterocyclic group (e.g., pyridyl, etc.).

5 Preferred substituents for the "optionally substituted heterocyclic group" represented by  $R^3$  include, for example, a halogen atom (e.g., chlorine, fluorine, etc.), a  $C_{1-6}$  alkyl group (e.g., methyl, ethyl, etc.), a  $C_{1-6}$  alkoxy group (e.g., methoxy, ethoxy, etc.), an aralkyloxycarbonyl group  
10 (e.g., a  $C_{7-12}$  aralkyloxy-carbonyl group such as benzyloxycarbonyl, etc.), an amino group, a mono- $C_{1-6}$  alkylamino group (e.g., methylamino, ethylamino, etc.) a di- $C_{1-6}$  alkylamino group (e.g., dimethylamino, diethylamino, etc.) etc.

15  $R^3$  is, for example, preferably (i) a hydrogen atom, (ii) an optionally substituted lower alkyl group, (iii) an optionally substituted aryl group, (iv) an optionally substituted 5- or 6-membered heterocyclic group, etc., more preferably, for example, (i) a hydrogen atom, (ii) a lower  
20 alkyl group, (iii) an optionally substituted  $C_{6-10}$  aryl group, (iv) an optionally substituted 6-membered nitrogen-containing heterocyclic group. The above substituents include, for example, a halogen atom, a  $C_{1-6}$  alkyl group, a  $C_{1-6}$  alkoxy group, an amino group, a mono- $C_{1-6}$  alkylamino  
25 group, a di- $C_{1-6}$  alkylamino group, etc. More preferably,  $R^3$

is, for example, a hydrogen atom, a phenyl group and a 2-, 3- or 4-pyridyl group, especially preferably is a hydrogen atom.

In the above-mentioned formulae, X represents  $\text{CHR}^4$ ,  
5  $\text{NR}^4$ , O or S in which  $\text{R}^4$  represents a hydrogen atom or an optionally substituted hydrocarbon group.

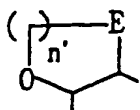
$\text{R}^4$  is preferably a hydrogen atom or an optionally substituted lower ( $\text{C}_{1-6}$ ) alkyl group, respectively. More preferred is a hydrogen atom.

10 X is preferably  $\text{CHR}^4$  in which  $\text{R}^4$  is as defined above, O or S. Or, X is preferably  $\text{CHR}^4$  or  $\text{NR}^4$  in which  $\text{R}^4$  is as defined above.

In the above formulae, Y represents C, CH or N. Y is preferably C or CH.

15 In the above-mentioned formulae, ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring.

The "5- to 7-membered oxygen-containing heterocyclic ring" includes 5- to 7-membered (preferably 5- or 6-  
20 membered) heterocyclic rings optionally having 1 or 2 kinds, 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms, in addition to carbon atoms and an oxygen atom. The above-mentioned heterocyclic ring is preferably a ring represented by the  
25 formula:

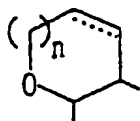


wherein E represents (i)  $\text{CH}_2\text{CH}_2$ , (ii)  $\text{CH}=\text{CH}$ , (iii)  $\text{CH}_2\text{O}$ ,  
 (iv)  $\text{OCH}_2$ , (v)  $\text{CH}_2\text{S}(\text{O})_{q'}$ , wherein  $q'$  represents an integer of  
 0 to 2, (vi)  $\text{S}(\text{O})_{q'}\text{CH}_2$  wherein  $q'$  is as defined above, (vii)  
 5  $\text{CH}_2\text{NH}$ , (viii)  $\text{NHCH}_2$ , (ix)  $\text{N}=\text{N}$ , (x)  $\text{CH}=\text{N}$ , (xi)  $\text{N}=\text{CH}$  or (xii)  
 $\text{CONH}$ ; and  $n'$  represents an integer of 0 to 2.

E is preferably (i)  $\text{CH}_2\text{CH}_2$ , (ii)  $\text{CH}=\text{CH}$ , (iii)  $\text{CH}_2\text{O}$ ,  
 (iv)  $\text{OCH}_2$ , (v)  $\text{CH}_2\text{NH}$ , (vi)  $\text{NHCH}_2$ , (vii)  $\text{N}=\text{N}$ , (viii)  $\text{CH}=\text{N}$  or  
 (ix)  $\text{N}=\text{CH}$ , especially preferably (i)  $\text{CH}_2\text{CH}_2$  or (ii)  $\text{CH}=\text{CH}$ .

10 Concretely, the above ring includes, for example, a 5-  
 membered oxygen-containing heterocyclic ring such as 2,3-  
 dihydrofuran, furan, 1,3-dioxole, oxazoline, isoxazole,  
 1,2,3-oxadiazole and oxazole and a 6-membered oxygen-  
 containing  
 15 heterocyclic ring such as 2H-3,4-dihydropyran, 2H-pyran,  
 2,3-dehydro-1,4-dioxane and 2,3-dehydromorpholine.

More preferably, the above ring is a ring represented  
 by the formula:



20 wherein n is as defined above.

Concretely, 2,3-dihydrofuran, furan, 2H-3,4-

dihydropyran and 2H-pyran are preferred.

Substituents which ring A may optionally have, include, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted lower alkynyl group, an optionally substituted lower alkenyl group, an optionally substituted aryl group, a lower alkoxy group (e.g., a C<sub>1-6</sub> alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.), an aryloxy group (e.g., a C<sub>6-10</sub> aryloxy group such as phenoxy, etc.), a lower alkanoyl group (e.g., formyl, a C<sub>1-6</sub> alkyl-carbonyl group such as acetyl, propionyl, butyryl, isobutyryl, etc.), an arylcarbonyl group (e.g., a C<sub>6-10</sub> aryl-carbonyl group such as benzoyl, naphthoyl, etc.), a lower alkanoyloxy group (e.g., formyloxy, a C<sub>1-6</sub> alkyl-carbonyloxy group such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.), an arylcarbonyloxy group (e.g., a C<sub>6-10</sub> aryl-carbonyloxy group such as benzoyloxy, naphthoyloxy, etc.), a carboxyl group, a lower alkoxycarbonyl group (e.g., a C<sub>1-6</sub> alkoxy-carbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, etc.), an aralkyloxy group (e.g., a C<sub>7-11</sub> aralkyloxy-carbonyl group such as benzyloxycarbonyl, etc.), a carbamoyl group, a

thiocarbamoyl group, a mono-, di- or tri-halogeno-lower alkyl group (e.g., a mono-, di- or tri-halogeno-C<sub>1-4</sub> alkyl group such as chloromethyl, dichloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, etc.), an oxo group, an amidino group, an imino group, an amino group, a mono-lower alkylamino group (e.g., a mono-C<sub>1-4</sub> alkylamino group such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g., a di-C<sub>1-4</sub> alkylamino group such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, methylethylamino, etc.), a 3- to 6-membered cyclic amino group optionally having 1 to 3 hetero atoms selected from, for example, oxygen, sulfur and nitrogen atoms, in addition to carbon atoms and one nitrogen atom (e.g., a 3- to 6-membered cyclic amino group such as aziridinyl, azetidiny, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidyl, morpholinyl, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, etc.), an alkylenedioxy group (e.g., a C<sub>1-3</sub> alkylenedioxy group such as methylenedioxy, ethylenedioxy, etc.), a hydroxyl group, a nitro group, a cyano group, a mercapto group, a sulfo group, a sulfinio group, a phosphono group, a sulfamoyl group, a monoalkylsulfamoyl group (e.g., a mono-C<sub>1-6</sub> alkylsulfamoyl group such as N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-

butylsulfamoyl, etc.), a dialkylsulfamoyl group (e.g., a di-C<sub>1-6</sub> alkylsulfamoyl group such as N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, etc.), an alkylthio group (e.g., a C<sub>1-6</sub> alkylthio group such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.), an arylthio group (e.g., a C<sub>6-10</sub> arylthio group such as phenylthio, naphthylthio, etc.), a lower alkylsulfinyl group (e.g., a C<sub>1-6</sub> alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc.), an arylsulfinyl group (e.g., a C<sub>6-10</sub> arylsulfinyl group such as phenylsulfinyl, naphthylsulfinyl, etc.), a lower alkylsulfonyl group (e.g., a C<sub>1-6</sub> alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, etc.), an arylsulfonyl group (e.g., a C<sub>6-10</sub> arylsulfonyl group such as phenylsulfonyl, naphthylsulfonyl, etc.), etc.

The above "lower alkyl group", "lower alkenyl group", "lower alkynyl group", "lower cycloalkyl group" and "aryl group" each may optionally have the same ones as the above-mentioned 1 to 5, preferably 1 to 3 substituents such as those "hydrocarbon group" may optionally have.

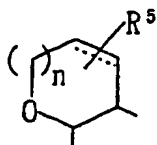
Preferred substituents which ring A may optionally have, include, for example, a halogen atom, an optionally substituted C<sub>1-6</sub> alkyl group, an optionally substituted C<sub>1-6</sub>



alkoxy group, a hydroxyl group, a nitro group, a cyano group, an optionally substituted amino group and an oxo group. For the substituents in these "optionally substituted C<sub>1-6</sub> alkyl group", "optionally substituted C<sub>1-6</sub> alkoxy group" and "optionally substituted amino group", for example, referred to are the substituents which mentioned-above "hydrocarbon group" may optionally have.

Ring A may have 1 to 4, preferably 1 or 2 substituents selected from those mentioned above at any substitutable positions, depending on the number of the carbon atoms constituting them. When the ring has two or more substituents, these substituents may be the same or different.

Ring A is, for example;



15

wherein  $n$  is as defined above; and  $R^5$  represents a hydrogen atom or 1 or 2 substituents selected from the "preferred substituents for ring A mentioned hereinabove. Among them, preferred is the one wherein  $R^5$  is a hydrogen atom or an optionally substituted lower (C<sub>1-6</sub>) alkyl. More preferred is the one wherein  $R^5$  is a hydrogen atom, which indicates unsubstituted ring A.

20

In the above-mentioned formulae, ring B represents an

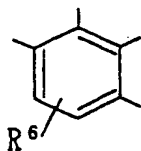
optionally substituted benzene ring.

The substituents which ring B may optionally have, include, for example, the "substituents" mentioned hereinabove for the "optionally substituted benzene ring".

5 Among others, the substituents on ring B are preferably a halogen atom or an optionally substituted lower ( $C_{1-6}$ ) alkyl group, more preferably a halogen atom or a lower ( $C_{1-6}$ ) alkyl group (especially, methyl). As for the substituents for the "optionally substituted lower ( $C_{1-6}$ ) alkyl group",  
10 for example, referred to are the same ones as the mentioned-above "hydrocarbon group" may optionally have.

Ring B may have one or two, preferably one substituent selected from those mentioned hereinabove, at any substitutable position. When ring B has two substituents,  
15 they may be the same or different.

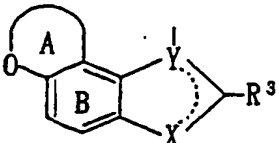
For example, ring B is preferably

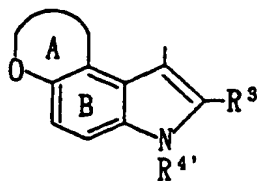
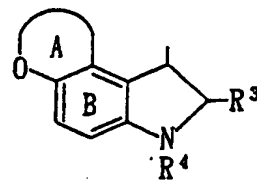
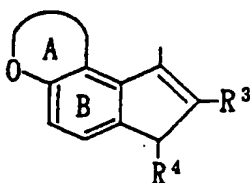
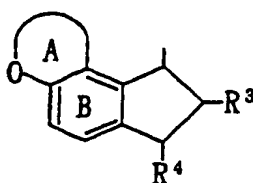


wherein  $R^6$  represents a hydrogen atom, a halogen atom, an optionally substituted lower ( $C_{1-6}$ ) alkyl group or an  
20 optionally substituted lower ( $C_{1-6}$ ) alkoxy group.  $R^6$  is preferably a hydrogen atom, a halogen atom or a lower ( $C_{1-6}$ ) alkyl group (especially, methyl). More preferably,  $R^6$  is a hydrogen atom.

In the above-mentioned formulae, m represents an integer of 1 to 4. Preferably, m is an integer of 1 to 3. More preferred is 2 or 3. Especially 2 is preferable.

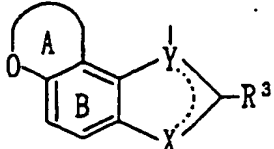
In the above-mentioned formulae, n represents an integer of 0 to 2. Preferably, n is an integer of 0 or 1. Especially 0 is preferable.

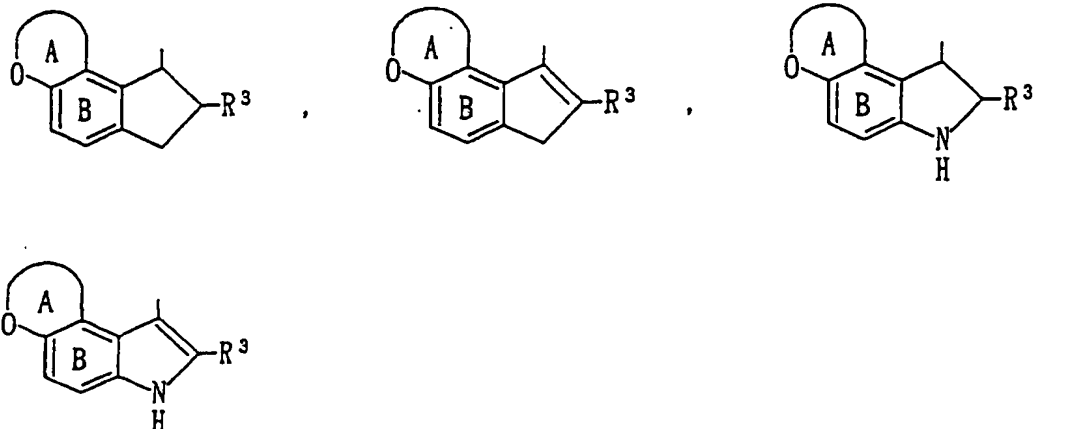
Examples of  include



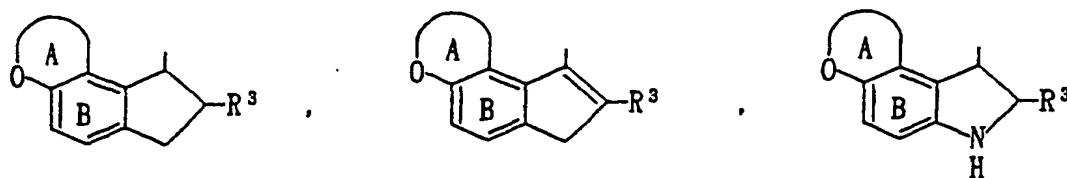
wherein  $R^{4'}$  represents an optionally substituted hydrocarbon group and the other symbols are as defined above.

$R^{4'}$  is preferably an optionally substituted lower ( $C_{1-3}$ ) alkyl group.

Preferred examples of  include

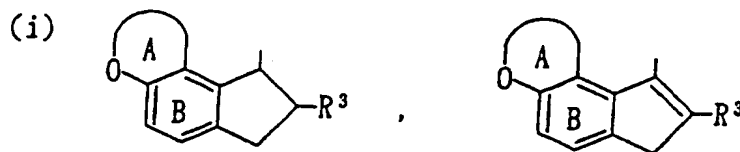


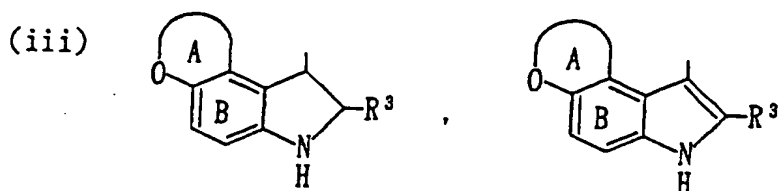
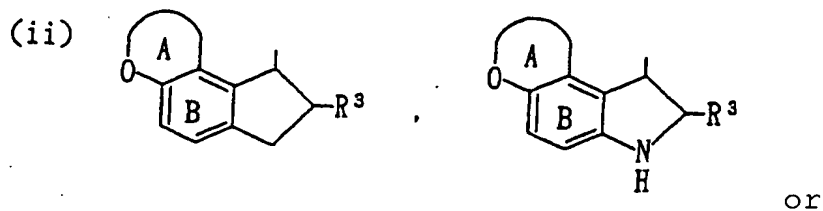
wherein the symbols are as defined above. Among them,  
5 preferred are



wherein the symbols are as defined above.

Further preferred are





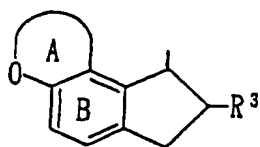
wherein the symbols are as defined above.

More preferred are



5

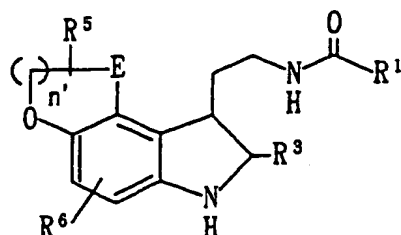
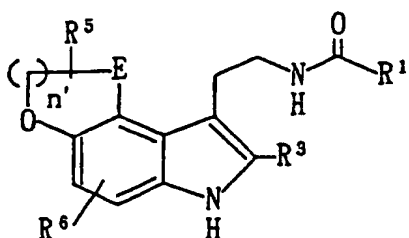
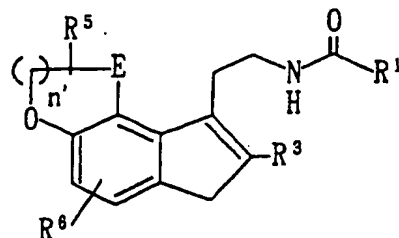
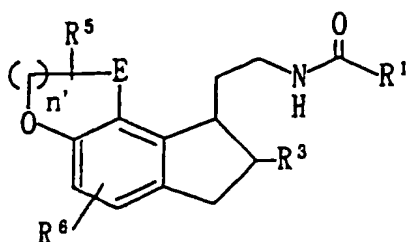
wherein the symbols are as defined above. Especially preferred is



wherein the symbols are as defined above.

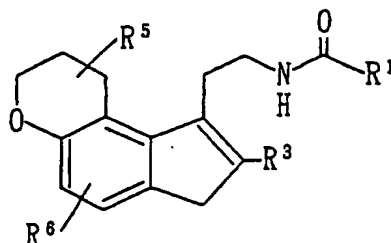
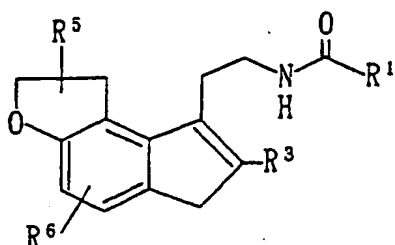
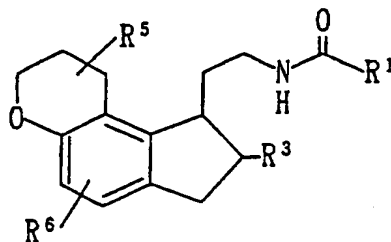
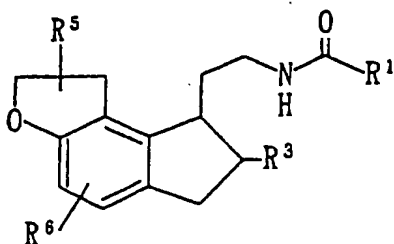
10

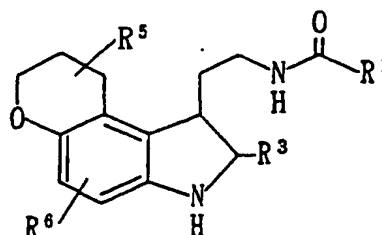
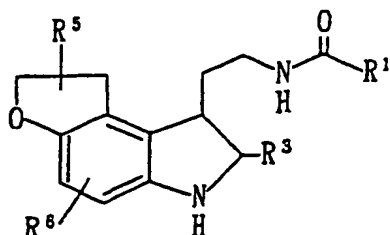
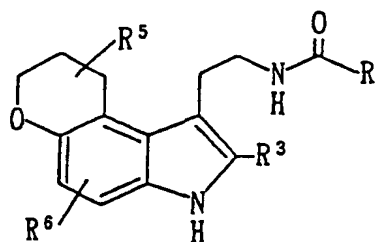
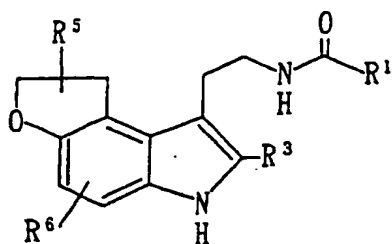
Example of the compound (I) include compounds having the following structural formulae.



wherein the symbols are as defined above.

Preferred examples of the compound (I) include, for example, compounds of the following formulae:





wherein the symbols are as defined above.

Also preferred examples of the compound (I) are the compound of the formula (I) wherein;

- 5             $R^1$  is (i) an optionally substituted lower alkyl group, (ii) an optionally substituted lower cycloalkyl group, (iii) an optionally substituted lower alkenyl group, (iv) an optionally substituted aryl group, (v) an optionally substituted mono- or di-lower alkylamino group, (vi) an
- 10 optionally substituted arylamino group or (vii) an optionally substituted, 5- or 6-membered nitrogen-containing heterocyclic group;

$R^2$  is a hydrogen atom or an optionally substituted lower ( $C_{1-6}$ ) alkyl group;

- 15             $R^3$  is (i) a hydrogen atom, (ii) an optionally substituted lower alkyl group or (iii) an optionally substituted aryl group; X is  $CHR^4$  or  $NR^4$  wherein  $R^4$  is a

hydrogen atom or a lower ( $C_{1-6}$ ) alkyl group optionally substituted by an oxo group;

Y is C, CH or N, provided that when X is  $CH_2$ , Y is C or CH;

5               is a single bond or a double bond;

ring A is an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;

ring B is an optionally substituted benzene ring; and m is 1 or 2.

10        More preferred is the compound wherein:

$R^1$  is (i) a  $C_{1-6}$  alkyl group optionally substituted by 1 to 4 substituents selected from the group consisting of a halogen and a  $C_{1-6}$  alkoxy group, (ii) a  $C_{3-6}$  cycloalkyl group, (iii) a  $C_{2-6}$  alkenyl group, (iv) a  $C_{6-10}$  aryl group

15        optionally substituted by 1 to 4 substituents selected from the group consisting of a  $C_{1-6}$  alkoxy group, a nitro group, a halogeno- $C_{1-6}$  alkyl-carbonylamino group and a halogen, (v) a mono- or di- $C_{1-6}$  alkylamino group, (vi) a  $C_{6-10}$  arylamino group optionally substituted by 1 to 3  $C_{1-6}$  alkoxy groups or  
20        (vii) a 6-membered nitrogen-containing heterocyclic group optionally substituted by one or two  $C_{7-11}$  aralkyloxy-carbonyl groups;

$R^2$  is a hydrogen atom or a lower ( $C_{1-6}$ ) alkyl group;

$R^3$  is (i) a hydrogen atom, (ii) a lower ( $C_{1-6}$ ) alkyl  
25        group or (iii) a  $C_{6-14}$  aryl group;

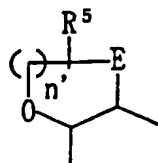


X is  $\text{CHR}^4$  or  $\text{NR}^4$  wherein  $\text{R}^4$  is a hydrogen atom or a lower ( $\text{C}_{1-6}$ ) alkyl group optionally substituted by an oxo group;

Y is C, CH or N, provided that when X is  $\text{CH}_2$ , Y is C or CH;

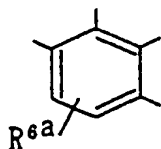
\_\_\_\_\_ is a single bond or a double bond;

ring A is



wherein the symbols are as defined above;

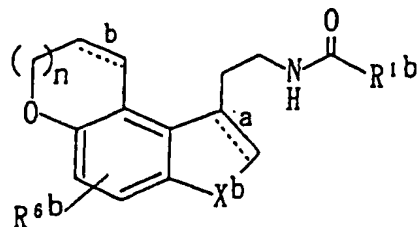
ring B is



wherein  $\text{R}^6\text{a}$  represents a hydrogen atom, a halogen atom or a lower ( $\text{C}_{1-6}$ ) alkyl group; and

m is 1 or 2.

Preferred among them is the compound represented by the formula:



wherein  $\text{R}^{1b}$  represents a  $\text{C}_{1-6}$  alkyl group,  $\text{R}^{6b}$  represents a

7hydrogen atom or a halogen atom, n represents 0 or 1,

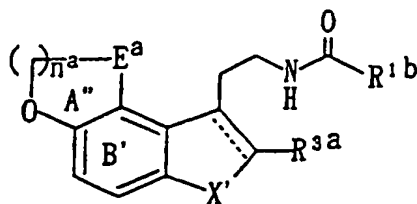
      b       ,

represents a single bond or a double bond,       a       represents

a single bond or a double bond when  $X^b$  is  $CH_2$ , and       a      

5 represents a single bond when  $X^b$  is NH; and a salt thereof.

Preferred among them is also the compound by the formula:



wherein  $R^{1b}$  is  $C_{1-6}$  alkyl,

10  $X'$  is  $CH_2$ , NH or NCHO,

$R^{3a}$  is a hydrogen atom or a phenyl group,

       is a single bond or double bond,

$E^a$  is  $CH_2CH_2$ ,  $CH=CH$ ,  $CH_2O$ ,  $CH=N$ , CONH or  $CH_2NH$ ,

$n^a$  is 0 or 1,

15 ring A'' is a 5- or 6-membered oxygen-containing heterocyclic ring which may be substituted by 1 or 2  $C_{1-6}$  alkyl optionally substituted by a hydroxy, and ring B' is a benzene ring which may be substituted by a halogen); and a salt thereof. Among them, the compound wherein        is a  
20 single bond ora double bond when  $X'$  is  $CH_2$  or NCHO, and        is a single bond when  $X'$  is NH is also preferred.

Preferable examples of the compound (I) include, N-[2-

(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butylamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide, N-[2-(5-fluoro-3,7,8,9-tetrahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide, N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]butylamide, N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide, N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]butylamide, N-[2-(4-fluoro-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butylamide, N-[2-(4-fluoro-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, (R)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butylamide, N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide, N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butylamide, N-[2-(7,8-dihydro-6H-indeno[4,5-d]-1,3-dioxol-8-yl)ethyl]propionamide, N-[2-(7,8-dihydro-6H-indeno[4,5-d]-1,3-dioxol-8-yl)ethyl]butylamide, N-[2-(2,3,8,9-tetrahydro-7H-indeno[4,5-b]-1,4-dioxyn-9-

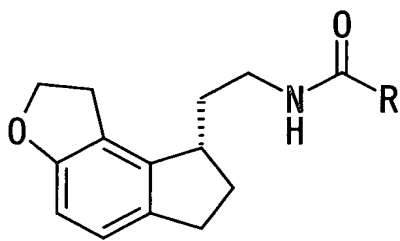
yl)ethyl]propionamide, N-[2-(2,3,8,9-tetrahydro-7H-indeno[4,5-b]-1,4-dioxyn-9-yl)ethyl]butylamide, N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide, N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]butylamide, N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, and N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butylamide.

More preferred are N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, N-[2-(5-fluoro-3,7,8,9-tetrahydrocyclopenta[f][1]-benzopyran-9-yl)ethyl]propionamide, N-[2-(5-fluoro-1,2,3,7,8,9-hexahydrocyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide, (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, (R)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butylamide, N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide, N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, N-[2-(1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butylamide, N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]propionamide, N-[2-(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-yl)ethyl]butylamide, N-[2-(7-phenyl-

1,6-dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,  
and N-[2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-  
yl)ethyl]butylamide.

Especially preferred are (S)-N-[2-(1,6,7,8-tetrahydro-  
5 2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, N-[2-  
(1,6,7,8-tetrahydro-2H-furo[3,2-e]indol-8-  
yl)ethyl]propionamide, N-[2-(1,6,7,8-tetrahydro-2H-  
furo[3,2-e]indol-8-yl)ethyl]butylamide, N-[2-(7-phenyl-1,6-  
dihydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide, N-  
10 [2-(7-phenyl-1,6-dihydro-2H-indeno[5,4-b]furan-8-  
yl)ethyl]butylamide, and N-[2-(1,6,7,8-tetrahydro-2H-  
indeno[5,4-b]furan-8-yl)ethyl]acetamide.

Especially preferred compound (I) is the compound  
represented by the formula:



15

wherein R is C<sub>1-6</sub> alkyl group (methyl, ethyl, propyl,  
isopropyl, butyl, isobutyl, sec-butyl, ter-butyl, pentyl,  
hexyl, etc.); and concretely, (S)-N-[2-(1,6,7,8-tetrahydro-  
2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide or (S)-N-[2-  
20 (1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-  
yl)ethyl]acetamide is preferred.

Salts of the compound (I) of the present invention

include, for example, pharmaceutically acceptable salts thereof. For example, mentioned are salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids. Preferred examples of salts with inorganic bases include, for example, alkali metal salts such as sodium salts and potassium salts, alkaline earth metal salts such as calcium salts and magnesium salts, as well as aluminium salts and ammonium salts. Preferred examples of salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine and N,N'-dibenzylethylenediamine. Preferred examples of salts with inorganic acids include, for example, salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid. Preferred examples of salts with organic acids include, for example, salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid or p-toluenesulfonic acid. Preferred examples of salts with basic amino acids include, for example, salts with arginine, lysine and ornithine. Preferred examples of salts with acidic amino acids include,

for example, salts with aspartic acid and glutamic acid.

Among others, preferred are pharmaceutically acceptable salts which include, for example, salts with inorganic acids such as hydrochloric acid, hydrobromic acid, 5 nitric acid, sulfuric acid and phosphoric acid, and salts with organic acids such as acetic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid and p-toluenesulfonic acid, when the compound (I) has basic functional groups; or 10 alkali metal salts such as sodium salts and potassium salts, and alkaline earth metal salts such as calcium salts and magnesium salts, and ammonium salts, when the compound (I) has acidic functional groups.

Compound (I) of the present invention may be hydrated 15 or non-hydrated.

Compound (I) can be obtained in accordance with, for example, a process disclosed in Japanese Patent No. 2884153 and like processes.

Physicochemical properties of compounds having a 20 melatonin receptor agonist activity suited for the percutaneous absorption preparations of the present invention include: moderate solubility to water (about 0.005 to about 10 mg/L) which allows the compound to be released from the formulation at an appropriate speed to 25 distribute in the skin and finally absorbed in the general

circulation, and partition ratio to oil (water/octanol partition coefficient: about 0.05 to about 10,000).

As for other conditions:

(1) those having a property that the compound does not  
5 become unstable in formulation;

(2) those having a property of not reacting with adhesive agents, skin permeation promoting agents used in formulation or generally used additives;

(3) those having a property of dissolving in about  
10 0.1% by weight or more in volatile solvents such as alcohol, acetone, ethyl acetate and the like which are generally used in production of formulation;

(4) those having a molecular weight of not more than about 1000; and

15 (5) those having a melting point of not more than about 300 °C are preferred.

The percutaneous absorption preparation of the present invention can be produced by processes generally used for producing percutaneous absorption preparations and like  
20 processes .

As for the form for the percutaneous absorption preparations of the present invention, it is preferred to use, for example, those providing excellent handling, adherence to skin, and percutaneous absorptivity by sealing  
25 bandage treatment method, and concretely, those in which a



so-called adhesive agent having adherence at ordinary temperatures is a base of a skin contact member, a plaster (skin plaster) in which an adhesive agent layer is formed on one side of a support member (backing layer) in view of the handling and the like.

In such a percutaneous absorption preparation, the compound having a melatonin receptor agonist activity serving as an active ingredient is preferably held by a skin contact member. Furthermore, while the skin contact member and the support member (backing layer) are made into one piece, the side not being in contact with the support member (backing layer) of the skin contact member may be protected by a protecting member such as release coated liner, or by making itself into a roll shape.

Furthermore, the skin contact member may not have cohesiveness. In such a case, the formulation is fixed by, for example, a tape and the like, thereby keeping the skin contact member and the skin in contact with each other.

The skin contact member is preferably principally made up of a compound having a melatonin receptor agonist activity which is an effective component, an adhesive agent and a skin permeation promoting agent. Furthermore, as is necessary, stabilizers, drug solubilizing agents, antibacterial agents, fillers, etc. may be contained.

It is preferred that the adhesive agent is made up of

pharmaceutical adhesive agents, such as conventionally used (meth)acrylic adhesive agents, rubber type adhesive agents, and silicone type adhesive agents which have cohesiveness at ordinary temperatures and will not cause a rash and the like by insuring keratin when it comes into contact with the skin surface. Among these, (meth)acrylic adhesive agents which will not cause a chemical reaction, are stable in quality and superior in air permeability and cohesiveness are most preferred.

10 As the (meth)acrylic adhesive agent, a self-crosslinking type (meth)acrylic copolymer containing soft segments and hard segments is used. For example, a copolymer obtained by polymerization of an about 50 to 80% by weight of (meth)acrylic acid ester and an about 20 to 15 50% by weight of one or two kinds of copolymerizable monomers is used. As such a (meth)acrylic acid ester, an ester obtained from acrylic acid or methacrylic acid, and a primary to tertiary alcohol having 2 to 18, preferably 4 to 12 carbon atoms can be used.

20 Concrete (meth)acrylic adhesive agents include a copolymer composed of 2-hexyl acrylate and acrylic acid, a copolymer composed of 2-ethylhexyl acrylate and hydroxyethyl acrylate, a copolymer composed of 2-ethylhexyl acrylate and vinylpyrrolidone, a copolymer composed of 2-ethylhexyl acrylate and 2-methoxyethyl acrylate, a 25

copolymer composed of 2-ethylhexyl acrylate and vinylpyrrolidone and acrylic acid, and the like.

As the rubber type adhesive agents, natural rubber, synthetic isoprene rubber, polyisobutylene, polyvinylether,  
5 polyurethane, polybutadiene, styrene-butadiene copolymer and the like are used.

As the silicone type adhesive agents, silicone rubbers such as polyorganosiloxane are used.

On the other hand, as the copolymerizable monomers,  
10 monomers having at least one unsaturated double bond involving the copolymerization reaction in the molecule, as well as having a functional group such as hydroxyl group, carboxyl group, amide group or amino group for its side chain can be used.

15 Examples of monomers having a hydroxyl group for its side chain include 2-hydroxyethyl (meth)acrylate, hydroxypropyl (meth)acrylate and the like.

Examples of monomers having a carboxyl group for its side chain include  $\alpha$ - $\beta$  unsaturated carboxylic acids such as  
20 (meth)acrylic acid, maleic acid monoalkylesters such as butyl maleate, maleic acid, fumaric acid, crotonic acid and the like.

Examples of the monomers having an amide group for its side chain include alkyl (meth)acrylamides such as  
25 acrylamide, dimethyl acrylamide and diethyl acrylamide,

alkyl ethers of methylol (meth)acrylamide such as butoxymethyl acrylamide and ethoxymethyl acrylamide, diacetone acrylamide, vinyl pyrrolidone and the like.

5 Examples of monomers having an amino group for its side chain include dimethylamino acrylate and the like.

Examples of monomer that can polymerize other than the above include (meth)acrylonitrile, vinyl acetate, vinyl propionate, N-vinyl-2-pyrrolidone, methylvinylpyrrolidone, vinylpyridine, vinylpyperidone, vinylpyrimidine, 10 vinylpiperazine, vinylpyrazine, vinylpyrrole, vinylimidazole, vinylcaprolactam, vinyloxazole, vinylformoline and the like.

As the copolymerizable monomers, monomers having at least one unsaturated double bond involving 15 copolymerization reaction in its molecule, as well as having a hydroxyl group which is a functional group for its side chain are preferred. Examples of which include hydroxyethylmetacrylate (HEMA), hydroxypropylmetaacrylate (HPMA) and the like.

20 The polymerizing monomers as described above may copolymerized by one or more kinds of monomers, however, from the view points of adhesiveness in the meaning of the cohesiveness property and releasability of the compound having melatonin receptor agonist activity included in the 25 skin contact member, those including at least one of the

carboxylic group-containing monomer and hydroxyl group-containing monomer as an essential component are preferred. Furthermore, these monomers are used for copolymerization with (meth)acrylic acid ester in the range of about 1 to about 50% by weight, preferably about 3 to about 20% by weight. If necessary, the above-exemplified other monomers, for example, vinyl monomers such as vinyl acetate and N-vinyl-2-pyrrolidone can be copolymerized with (meth)acrylic acid in the range of not more than about 40% by weight, preferably not more than about 30% by weight.

The copolymers based on (meth)acrylic acid ester as described above are usually prepared by mixing the above-mentioned monomers in the presence of a polymerization primer and conducting solution polymerization. The solution polymerization can be conducted by adding ethyl acetate or other polymerization solvent to predetermined amounts of various monomers, and allowing the resultant mixture to react in a reactor equipped with a stirrer and a reflux condenser, in the presence of a polymerization initiator of azobis type or peroxide type, under the nitrogen atmosphere, at the temperature of about 70 to about 90 °C for about 8 to about 40 hours. The monomer may be introduced either by single loading or separated loading.

It is preferred that the ratio of the (meth)acrylic acid ester in the constituents of the copolymer based on

the (meth)acrylic ester is about 50% by weight or more.

Examples of the above-mentioned azobis type polymerization initiator include 2,2-azobis-iso-butyronitrile, 1,1'-azobis(cyclohexane-1-carbonitrile),  
5 2,2'-azobis(2,4-dimethylvalerinitorile) and the like.

Examples of the above-mentioned peroxide type polymerization initiator include lauroyl peroxide, benzoyl peroxide, di(tert-butyl)peroxide and the like.

As the rubber type adhesive agents, natural rubber,  
10 synthetic isoprene rubber, polyisobutylene, polyvinylether, polyurethane, polybutadiene, styrene-butadiene copolymer, styrene-isoprene copolymer and the like are used.

As the silicone type adhesive agent, silicone rubbers such as polyorganosiloxane are used.

15 The skin permeation promoting agent is an agent which mainly acts on keratin which is the surface of the skin to facilitate permeation of the drug through the skin, thereby enabling efficient percutaneous absorption.

Generally, keratin is formed by plural layers of cell  
20 membranes overlapped with one after another, each cell membrane consisting of lipid bilayer generated as a result of metabolism of surface cells. Owing to this, harmful substances are prevented from easily entering the body. This is also the reason why drugs are difficult to be  
25 absorbed percutaneously in the manner usually used.

Therefore, the main target of the skin permeation promoting agent is a lipid bilayer.

As the substance that acts on a lipid bilayer, strong surfactants such as detergent, solvents such as chloroform, ethers, benzenes and the like can be considered, however, these are not preferable because they stimulate and break a lipid bilayer, leading harmful actions.

Preferable properties of the skin permeation promoting agent include:

(1) improving fluidity of the membranes of a lipid bilayer;

(2) spreading a clearance of the layer structure of membrane by moisturizing the same;

(3) improving solubility of the compound having a melatonin receptor agonist activity in the skin contact member, to thereby increase the release speed from the formulation.

As the promoting agent that satisfies these properties and has a drug release characteristic that gives a one-peak blood-drug-concentration-time profile similar to the melatonin secretion pattern, the following (A), (B), (C) and the like can be exemplified. The percutaneous absorption preparation of the present invention contains one or more kinds selected from these three types of promoting agents, and preferably contains three kinds (A),

(B) and (C).

(A) Lipid soluble absorption promoting agents. More preferably fatty acid esters composed of a fatty acid having 6 to 22 carbon atoms and an alcohol having 1 to 12 carbon atoms, and the like.

(B) Water soluble absorption promoting agents. More preferably polyhydric alcohols and the like.

(C) Nonionic surfactants. More preferably, fatty acid amides and the like such as lauric diethanolamide and compounds containing the same.

Examples of the above-mentioned fatty acids having 6 to 22 carbons include those having 6 to 22 carbons (for example, 10 to 22 carbons, more preferably 10 to 20 carbons) such as caproic acid, enanthic acid, caprylic acid, monocapric acid, oleic acid, lauric acid, undecylenic acid, myristic acid, isostearic acid, linoleic acid, palmitic acid, margaric acid, stearic acid, hexadecenoic acid, and the like.

Examples of the above-mentioned alcohols having 1 to 12 carbon atoms include methyl alcohol, ethyl alcohol, propanol, isopropanol, butanol, t-butanol, hexanol, octanol and the like. The "fatty acid" used in this context means natural or synthetically obtainable fatty acids in the same range as described above.

Therefore, examples of the above-mentioned fatty acid



esters include isopropyl adipate, isopropyl myristate, diester sebacate, isopropyl palmitate, isopropyl stearate, butyl stearate, octyldodecyl myristate, hexyl laurate, octyl palmitate, ethyl oleate, butyl myristate and the like.

5 Among these, isopropyl myristate, diester sebacate, isopropyl palmitate, butyl myristate and the like are preferred, and isopropyl myristate is particularly preferred.

Examples of the above-mentioned polyhydric alcohols  
10 include ethylene glycols (ethylene glycol, diethylene glycol, triethylene glycol), low molecular glycols such as glycerin, propyleneglycol and 1,3-butyleneglycol, high molecular glycols having a molecular weight of about 200 to about 6,000 such as polyethyleneglycol and polypropylene  
15 glycol, and the like, and among these ethylene glycols, propyleneglycol, 1,3-butyleneglycol, glycerin, polyethyleneglycol and the like are preferred, and propylene glycol and polyethylene glycol (molecular weight of about 200 to about 1000) are particularly preferred.

20 As the nonionic surfactant, for example, polyoxyethylene fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene glyceryl fatty acid esters, polyoxyethylene alkyl ethers, polyoxyethylene alkylaryl ethers, glyceryl monooleate, glyceryl monolaurate, glyceryl  
25 monostearate, sorbitan monomyristate, sorbitan

monopalmitate, sorbitan monooleate, polyoxyethylene (5)  
sorbitan monooleate, polyoxyethylene (20) sorbitan  
monooleate, derivatives of polyoxyethylene castor oil,  
block polymer type nonionic surfactants (e.g., pluronic, L-  
5 62, L-64, F-68, etc.), polyhydric alcohol fatty acid esters  
(e.g., glyceryl monooleate, glyceryl monolaurate, glyceryl  
monostearate, glyceryl monomyristate, glyceryl  
monopalmitate, glyceryl dioleate, glyceryl dilaurate,  
glyceryl distearate, glyceryl dimyristate, glyceryl  
10 dipalmitate, propylene glycol monocaprylate, caprylic /  
capric triglyceride, etc.), fatty acid esters of  
polyglycerin (for example, fatty acid esters of triglycerin  
(e.g., triglyceryl oleate, triglyceryl laurate, triglyceryl  
stearate, triglyceryl myristate, triglyceryl palmitate),  
15 fatty acid esters of tetraglycerin (e.g., tetraglyceryl  
oleate, tetraglyceryl laurate, tetraglyceryl stearate,  
tetraglyceryl myristate, tetraglyceryl palmitate), fatty  
acid esters of pentaglycerin (e.g., pentaglyceryl oleate,  
pentaglyceryl laurate, pentaglyceryl stearate,  
20 pentaglyceryl myristate, pentaglyceryl palmitate), fatty  
acid esters of hexaglycerin (e.g., hexaglyceryl oleate,  
hexaglyceryl laurate, hexaglyceryl stearate, hexaglyceryl  
myristate, hexaglyceryl palmitate), fatty acid esters of  
heptaglycerin (e.g., heptaglyceryl oleate, heptaglyceryl  
25 laurate, heptaglyceryl stearate, heptaglyceryl myristate,

heptaglyceryl palmitate), fatty acid esters of decaglycerin (e.g., decaglyceryl oleate, decaglyceryl laurate, decaglyceryl stearate, decaglyceryl myristate, decaglyceryl palmitate), and the like), fatty acid amides (oleic

5 diethanolamide, myristic diethanolamide, stearic diethanolaminoethylamide, vinylpyrrolidone, lauric diethanolamide or substances containing the same, coconut fatty acid diethanolamide and the like), stearic diethylaminoethylamide, stearic dimethylaminopropylamide, 10 lauric derivative quaternary ammonium salt, benzalkonium chloride aqueous solution, and the like) can be exemplified.

Among these, fatty acid amides, fatty acid esters of polyhydric alcohol, fatty acid esters of polyglycerin are preferred, and in particular, fatty acid amides such as 15 lauric diethanolamide or substances containing the same (skin permeation promoting agent containing the same) and coconut fatty acid diethanolamide are further preferred.

If required, antioxidants, a filler, a drug solubilizing agent, an antibacterial agent, a skin 20 stimulation reducing agent, etc. may be added to the preparation of the present invention in addition to the above mentioned additives.

As the above antioxidant, vitamin E, vitamin C and the like can be exemplified.

25 As the above filler, kaolin, bentonite, titanium

dioxide, silicon dioxide and the like can be exemplified.

As the above drug solubilizing agent,  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin,  $\gamma$ -cyclodextrin and the like can be exemplified.

5 As the above antibacterial agent, benzalkonium chloride, benzoic acid, methyl-p-hydroxybenzoate and the like can be exemplified.

As the skin stimulation reducing agent, silicic anhydride can be exemplified.

10 In addition, other absorption promoting agents can be added. As the other absorption promoting agents, polyprenylazacycloalkanes (for example, 1-dodecylazacycloheptane-2-on and the like), oils and fats (for example, olive oil, castor oil, jojoba oil, corn  
15 embryo oil, sunflower oil, coconut oil, squalane, squalene, orange oil, mineral oil) can be exemplified.

Preferred skin permeation promoting agent comprises one or more kinds of fatty acid esters, polyhydric alcohols and nonionic surfactants. And most preferred skin  
20 permeation promoting agent is comprises all of a fatty acid ester, a polyhydric alcohol and a nonionic surfactant. A preferred fatty acid ester is isopropyl myristate, isopropyl palmitate, butyl myristate or diethyl sebacate. And a preferred polyhydric alcohol is ethylene glycol,  
25 propylene glycol, 1,3-butylene glycol, glycerin or

polyethylene glycol. A most preferred polyhydric alcohol is propylene glycol or polyethylene glycol. Particularly, it is preferred to blend silicon dioxide serving as a filler together with polyethylene glycol having a molecular weight of about 200 to about 1000, because the "stringiness(stickiness)" of adhesive agent is improved. Furthermore, a preferred nonionic surfactant is a fatty acid amide, a fatty acid ester of polyhydric alcohol or a fatty acid ester of polyglycerin. A most preferred nonionic surfactant is a fatty acid amide. A preferred fatty acid amide of that time is lauric diethanolamide or substances containing the same.

A most preferred fatty acid amide is lauric diethanolamide.

The formulation of the present invention improves the solubility in the skin contact member of the compound having a melatonin receptor agonist activity, and thus satisfies the releasability from the formulation.

When blending a compound having a melatonin receptor agonist activity in a skin contact member, it is preferred that the compound is blended in such a proportion that the action of the skin permeation promoting agent is fully spread out, facilitating permeation of the compound having a melatonin receptor agonist activity.

For example,

(1) A content of a compound having a melatonin receptor agonist activity with respect to the whole skin contact member is about 0.01 to about 70% by weight, more preferably about 10 to about 60% by weight, and further preferably about 20 to about 50% by weight;

(2) A content of a skin permeation promoting agent with respect to the whole skin contact member is about 0 to about 70% by weight, more preferably about 10 to about 60% by weight, and further preferably about 20 to about 50% by weight;

In the case where the skin permeation promoting agent contains of one or more kinds of a fatty acid ester, a polyhydric alcohol and a nonionic surfactant, individual weights of the fatty acid ester, the polyhydric alcohol and the nonionic surfactant in the skin contact member are, about 0 to about 70% by weight, and preferably about 1 to about 30% by weight (about 1 to about 15% by weight is preferred for the nonionic surfactant). In the case where the skin permeation promoting agent contains all of a fatty acid ester, a polyhydric alcohol and a nonionic surfactant, the blend proportion of the polyhydric alcohol is about 1/10 to about 10 times in weight, more preferably about 1/2 to about 5 times in weight, most preferably about once in weight of that of the fatty acid ester based on the blend weight of the fatty acid ester. Furthermore, the blend

proportion of the nonionic surfactant is about 1/50 to about 10 times in weight, more preferably about 1/20 to about 2 times in weight, and most preferably about 1/4 of that of the fatty acid ester

- 5 (3) A content of adhesive agent with respect to the whole skin contact member is about 5 to about 98% by weight, preferably about 10 to about 60% by weight, and more preferably about 20 to about 50% by weight;

Materials such as anti-oxidant, filler, drug  
10 solubilizing agent, antibacterial agent as described above can be blended in a skin contact member as other ingredients as is necessary. These components are added within the range that will not deteriorate the adhesiveness of the skin contact member and the effect of the skin  
15 permeation promoting agent, and the amount of blend thereof is about 0.01 to about 50% by weight, preferably about 1 to about 20% by weight, more preferably about 1 to about 10% by weight.

A plaster which is one embodiment of the formulation  
20 of the present invention can be obtained by pasting a support member (backing layer) on one surface of the adhesive agent layer and a release liner on the other surface of the adhesive agent layer.

As the support member (backing layer) of the plaster,  
25 any materials can be available insofar as they have an

effect of preventing water volatilization and moisturizing a skin which are necessary to allowing the active ingredient in the formulation according to the present invention to be absorbed efficiently after administration, and they enable patients to easily affix the present formulation on their skins and will not give abnormal feeling even after a long time of affixing. For example, a film formed of polyethylene, polypropylene, cellulose acetate, ethyl cellulose, polyethylene terephthalate, vinyl acetate-vinyl chloride copolymer, plastic poly(vinyl chloride), polyurethane, polyolefin or poly(vinylidene chloride) or an aluminum foil having a thickness of about 50 to about 200  $\mu\text{m}$  can be exemplified. These may be used in the form of a single layer sheet (film) or a lamination sheet, and woven or nonwoven fabric using materials other than aluminum foil can also be used.

As for the release liner, since the release liner is used as a "cover" for preventing the active ingredient in the present percutaneous absorption formulation from coming into contact with other object to pollute the same, or from being scraped to be impaired before use, any material is available insofar as a patient can easily remove it when using the present formulation and the skin contact member after removal of the release liner still keeps the condition before being covered with the release liner. For



example, siliconized polyethylene terephthalate film, paper, polyester, low density polyethylene, high density polyethylene, polypropylene, polystyrene, polyamide, nylon, polyvinyl chloride and the like having a thickness of 50 to  
5 about 100  $\mu\text{m}$  can be used.

The skin contact member can be formed by dissolving a composition containing an adhesive agent, a skin permeation promoting agent and a compound melatonin receptor agonist activity in an appropriate solvent, applying the resultant  
10 adhesive-containing solution on a supporting member (backing layer), and removing the solvent by drying.

As a manufacturing method of a plaster which is one embodiment of the formulation according to the present invention, a method in which a skin contact member is applied on a supporting member and a release liner is  
15 pasted on the surface of the skin contact member, and a method in which a skin contact member is applied on a release liner and a supporting member is pasted on the surface of the skin contact member can be exemplified. For  
20 application of the skin contact member, a solution in which a composition of a skin contact member is dissolved or a dispersed solution in which a part of the composition is dispersed is prepared by adding a variety of skin permeation promoting agents into a high concentration  
25 solution of the adhesive agent dissolved in an easily

volatile solvent dispersion solution and mixing them well,  
and adding the compound having melatonin receptor agonist  
activity of the present invention and mixing them well. As  
an easily volatile solvent which preferred in this case,  
5 those easily vaporize under appropriated dry condition  
(typically, the condition of heating for 1 hour at 50°C or  
the condition of placing at room temperature for all day  
and night) and will not remain in the skin contact member  
which is a final product or will not be harmful on a  
10 living body even if a small amount remains are selected.  
For example, mixture solutions in which about 0 to about  
500% by weight of isopropyl alcohol or acetone is contained  
in ethyl alcohol or ethyl acetate can be used.

It is preferred that the concentration of the adhesive  
15 agent in the solvent is high for the purpose of improving  
the application efficiency, however, too high concentration  
is not preferred for achieving uniform application.

Concentration for use is in the range of about 10% by  
weight to about 500% by weight and preferably about 20% by  
20 weight to about 150% by weight. Concentrations in solvent  
of constituents of skin contact member other than the  
adhesive agent are automatically determined when the blend  
proportions with respect to the adhesive are determined.

Since it is preferred that the compound having a melatonin  
25 receptor agonist activity is dissolved as much as possible,

a method in which of the compound is previously dissolved in an easily volatile solvent at high concentration and then added as a solvent solution is preferably applied.

Examples of the preferred easily volatile solvent include

5 the solvents used for dissolving the above-mentioned adhesive agent which will not remain in the skin contact member after drying, acetone, ethyl alcohol, methyl alcohol and the like. Acetone or ethyl acetate is preferred.

Concentration of the compound having a melatonin receptor

10 agonist activity in the solvent is selected to be supersaturation or concentrations nearly supersaturation.

As such a concentration, about 1 to about 20% by weight is used. In the case where the amount of blend of the

compound having a melatonin receptor agonist activity is

15 large, a part of the compound will not dissolve. However, also in this case, since it is preferred that the

individual particles are microparticles, powder of the compound having a melatonin receptor agonist activity is grained well before dissolving it in the solvent.

20 As the application method, a method including: fixing a supporting member (backing layer) or a release liner on a uniform plate such as glass plate; dropping a solution of a composition of a skin contact member in solvent thereon; spreading the solution by means of a roller such as a

25 commercially available applicator (casting device) (Baker

Applicator; Yoshimitsu Seiki) in such a condition that the solvent is spread into a uniform thickness; and thereafter placing it at room temperature for all day and night to evaporate the solvent. As the evaporating condition,  
5 heating for 30 minutes at 50°C in the initial stage may be used because it makes it possible to rapidly evaporate the solvent. The method as described above is a method for applying a relatively small amount, however, rotary continuous manufacturing machine that have been improved  
10 for mass production and generally used can be used. The thickness obtainable by dropping the solution in solvent of the composition of the skin contact member and spreading the same by means of a roller in such a condition that leads a uniform thickness is determined to be larger than  
15 the thickness of the skin contact member in contemplation of the volume of the solvent that is inversely calculated from the concentration. The thickness of the skin contact member is in the range of about 0.01 mm to about 5 mm, preferably about 0.05 mm to about 1 mm.

20 The formulation according to the present invention can be cut into pieces of appropriate size that can achieve the object prior to use.

The blend amount of the compound having a melatonin receptor agonist activity in the formulation of the present  
25 invention is not particularly limited insofar as the

compound is absorbed into the blood from the skin after administration, the blood concentration of the active ingredient is less than the concentration that leads a side effect, and the effective concentration can be kept for a long time. The blend amount of the compound having a melatonin receptor agonist activity is, for example, about 0.1 to about 60% by weight, preferably about 0.1 to about 20% by weight, more preferably about 1 to about 10% by weight of the total weight of the formulation. In the case where the formulation of the present invention is a plaster, blend amount of the compound having a melatonin receptor agonist activity per unit area of the skin contact region is, for example, about 0.01 to about 100 mg/cm<sup>2</sup>, preferably about 1 to about 100 mg/cm<sup>2</sup>, more preferably about 2 to about 50 mg/cm<sup>2</sup>, further preferably about 5 to about 10 mg/cm<sup>2</sup>. Typical effective concentration of the compound having a melatonin receptor agonist activity which is less than the concentration that leads a side effect is about 0.5 to about 1,000 ng/mL, more particularly about 1 to about 500 ng/mL.

Administration (affix) frequency for the formulation of the present invention is, for example, once every 1 to 7 days, preferably once every 1 to 3 days, more preferably once a day. Administration period for the formulation of the present invention is usually one month to five years,

and may be administered for a longer period so as to prevent development of the symptom. The administration period is preferably 3 months to four years, more preferably 6 months to two years. During such long period administration, the formulation of the present invention can be readily administered without putting a load on a patient.

In the case where the formulation of the present invention is a patch or a tape, the formulation may be cut into a convenient size and one or more pieces may be affixed on the same site or different sites on the body. The site to affix the formulation is not particularly limited, however, sites with little body hair are preferable and, for example, the formulation is affixed to the arm region inside, back, femoral region inside, and the like. Among these, the arm region is preferred.

It is preferable for a blood concentration pattern of a compound having a melatonin receptor agonist activity to resemble a secretion pattern of melatonin of a normal person. That is, as reported in Journal of Clinical Endocrinology and Metabolism 73: 1276-1280 (1991), melatonin secretion of a normal person rises in the night, and the melatonin concentration in the blood represents a one-peak pattern from the evening to the morning. Therefore, it is desirable for blood-drug-concentration-time-profile

to draw a one-peak pattern from the evening to the morning  
(within 12 hours after administration).

In this case, a preferred timing of administration of  
the absorption agent is in the evening or before going to  
5 bed (between 6 hours before bedtime or just before bedtime).

It is preferred for the peak of the blood  
concentration to appear in about 10 hours after  
administration.

It is preferable for the effective concentration of  
10 the compound to be maintained until about one to two hours  
before getting up and be damped afterwards. A duration  
time of effective concentration corresponds to a sleep time,  
and is preferably about 6 to about 12 hours.

The formulation of the present invention is useful for  
15 a pharmaceutical product because it has low toxicity and  
causes little side effect.

Dosage of the formulation of the present invention  
varies according to the type and content of the compound  
having a melatonin receptor agonist activity which is a  
20 principal component, dosage form, duration time of release  
of the compound having a melatonin receptor agonist  
activity, objective disease, objective animal and the like,  
however, it can be an effective amount of the compound  
having the melatonin receptor agonist activity. A single  
25 dosage of the compound having a melatonin receptor agonist

activity which is a principal component can be selected appropriately from, for example, the range of about 0.05 mg to 10 mg/kg body weight per adult person, preferably from a range of about 0.1 mg to 3mg/kg body weight per adult person.

The formulation of the present invention acts as a melatonin agonist or antagonist for mammals (for example, mouse, rat, hamster, rabbit, cat, dog, cow, sheep, monkey, human); and is useful as a melatonin receptor affinity composition, in particular, as a composition having a melatonin receptor agonist activity; and can be used for prevention and treatment of sleep-awake rhythm disorder, jet lag (jetlag), abnormality of physical condition by three change duty, severe depression of a season, genital and neuroendocrine disease, senile dementia, Alzheimer's disease, various disorders associated with aging (for example, antiaging), cerebral circulation disorder (for example, cerebral stroke), head injury, marrow damage, stress, epilepsia, cramp, uneasiness, depression, Parkinson's disease, high blood pressure, glaucoma, cancer, insomnia, diabetes and the like; and is also effective for immunoregulation, enhancement of cognition, ataractic or ovulation adjustment (for example, sterilization). The formulation of the present invention is used, for example, as a biological rhythm adjustment agent, preferably a



therapeutic agent for somnipathy (for example, sleep leading agent and the like), sleep-awake rhythm adjustment agent (including sleep-awake rhythm adjusting action), and a prevention and treatment agent for time zone change syndrome, a so-called jet lag (jetlag). For instance, in the case of treatment of a somnipathist, a formulation of the present invention containing an about 1 to about 10% by weight of an active ingredient is applied on inside of the arm once a day for one month.

Furthermore, the formulation of the present invention may be used, as appropriate, in combination with an appropriate amount of other active agents other than the compound having a melatonin receptor agonist activity (for example, benzodiazepinic drugs such as triazolam, diazepam, alprazolam, estazolam which are benzodiazepine compounds, non-benzodiazepinic drugs such as zolpidem, zalepron, zopiclone, brotizoram and the like, sleep rhythm adjustment agents such as butoctamide which is a fatty acid derivative or its salt, hypnotics such as cis-9,10-octadecenoamide).

#### BEST MODE FOR CARRYING OUT THE INVENTION

In the following , the present invention will be further explained while referring to test examples and comparative examples, however it is to be noted that these examples are not intended to limit the present invention.

## Examples

## Example 1

## [Table 1]

Composition of skin contact member	Percentage with respect to adhesive layer
(Adhesive agent)	
Self-crosslinking acrylic copolymer	47.5%
(Skin permeation promoting agent)	
Lauric diethanolamide	5.0%
Isopropyl myristate	20.0%
Propyleneglycol	20.0%
(Active ingredient)	
Compound A	7.5%

- 5 To a solution of 45% (w/w) of self-crosslinking acrylic copolymer (DuroTak™ 87-2979; National Starch & Chemical) in 8:2 (ratio in volume) ethyl acetate/isopropanol, lauric diethanolamide (AMINONE™ L-02; KAO Corporation Chemicals), isopropyl myristate,
- 10 propyleneglycol and (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide (referred to as Compound A) were added in the respective blend ratios of 5.0% by weight, 20.0% by weight and 7.5% by weight of the total weight of the skin contact member and mixed well, and
- 15 5.6 g of this mixture solution was dropped on a fluoropolymer-treated polyester film (Scotchpak™ 1022; product of 3M, thickness:75 μm, total area including a

merge part:450 cm<sup>2</sup>) spread on a plate of a casting device  
(Baker applicator: Yoshimitsu Seiki), and spread so that  
the thickness after drying will be 0.1 mm by means of a  
roller. Thereafter the solvent was air dried at room  
5 temperature for all day and night, and a support member  
(backing layer, polyethylene film, CoTran™ 9720; product  
of 3M, thickness:76μm) was pasted on the surface opposite  
to the skin contact surface, thereby obtaining a  
percutaneous absorption preparation of the present  
10 invention.

#### Example 2

[Table 2]

Composition of skin contact member	Percentage with respect to adhesive layer
(Adhesive agent)	
Self-crosslinking acrylic copolymer	53.0%
(Skin permeation promoting agent)	
Lauric diethanolamide	5.0%
Isopropyl myristate	20.0%
Propyleneglycol	20.0%
(Active ingredient)	
Compound A	2.0%

To a solution of 45% (w/w) of self-crosslinking  
15 acrylic copolymer (DuroTak™ 87-2979; National Starch &  
Chemical) in 8:2 (ratio in volume) ethyl  
acetate/isopropanol, lauric diethanolamide (AMINONE™ L-02;

KAO Corporation Chemicals), isopropyl myristate, propyleneglycol and Compound A were added in the respective blend ratios of 5.0% by weight, 20.0% by weight, 20.0% by weight and 2.0% by weight of the total weight of the skin contact member and mixed well, and a percutaneous absorption preparation of the present invention was obtained in the same condition and manner as Example 1.

#### Example 3

A composition in which a self-crosslinking acrylic copolymer which is an adhesive agent, lauric diethanolamide and Compound A which is an active ingredient are mixed in the proportion of 93:5:2 (w/w) was prepared, and a percutaneous absorption preparation of the present invention was obtained in the same condition and manner as Example 1.

#### Example 4

[Table 3]

Composition of skin contact member	A	B	C
	Percentage with respect to adhesive layer		
(Adhesive agent)			
Self-crosslinking acrylic copolymer	58.0	73.0	73.0
(Skin permeation promoting agent)			
Lauric diethanolamide	0.0	5.0	5.0
Isopropyl myristate	20.0	0.0	20.0
Propyleneglycol	20.0	20.0	0.0
(Active ingredient)			
Compound A	2.0	2.0	2.0

As shown in [Table 3], skin contact member compositions of three prescriptions (Rp. A to C) each excluding one of the three kinds of skin permeation promoting agents in Example 2 were prepared, and percutaneous absorption preparations of the present invention were prepared in the same manner as Example 1.

Example 5

A percutaneous absorption preparation of the present invention was prepared in the same manner as Example 1 in such a composition that in place of propyleneglycol in Example 1, the same amount of 1,3-butyleneglycol is blended.

Example 6

A percutaneous absorption preparation of the present invention was prepared in the same manner as Example 1 in

such a composition that in place of propyleneglycol in Example 1, the same amount of polyethyleneglycol having a molecular weight of 400 is blended.

Example 7

5           A percutaneous absorption preparation of the present invention was prepared in the same manner as Example 1 in such a composition that in place of isopropyl myristate in Example 1, the same amount of isopropyl palmitate is blended.

10          Example 8

          A percutaneous absorption preparation of the present invention was prepared in the same manner as Example 1 in such a composition that in place of isopropyl myristate in Example 1, the same amount of butyl myristate is blended.

15          Example 9

          A percutaneous absorption preparation of the present invention was prepared in the same manner as Example 2 in such a composition that in place of isopropyl myristate in Example 2, the same amount of diethyl sebacate is blended.

20          Example 10

          A percutaneous absorption preparation of the present invention was prepared in the same manner as Example 2 in such a composition that in place of Compound A in Example 1, the same amount of N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide is blended.

25

## Example 11

A percutaneous absorption preparation of the present invention was prepared in the same manner as Example 1 in such a composition that in place of lauric diethanolamine  
 5 in Example 1, the same amount of coconut fatty acid diethanol amide is blended.

## Example 12

[Table 4]

Composition of skin contact member	Percentage with respect to adhesive layer
(Adhesive agent)	
Self-crosslinking acrylic copolymer	68.0%
(Skin permeation promoting agent)	
Lauric diethanolamide	10.0%
Isopropyl myristate	10.0%
Polyethyleneglycol 600	10.0%
(Filler)	
Silicon dioxide	20.0%
(Active ingredient)	
Compound A	2.0%

10 To a solution of 41% (w/w) of self-crosslinking acrylic copolymer (DuroTak<sup>TM</sup>387-2516; National Starch & Chemical) in 8:2 (ratio in volume) ethyl acetate/isopropanol, lauric diethanolamide (AMINONE<sup>TM</sup> L-02; KAO Corporation Chemicals), isopropyl myristate,  
 15 polyethyleneglycol 600, silicon dioxide and Compound A were added in the respective blend ratios of 10.0% by weight,

10.0% by weight, 10.0% by weight, 20.0% by weight and 2.0%  
by weight of the total weight of the skin contact member  
(120%) and mixed well, and a percutaneous absorption  
preparation of the present invention was obtained in the  
5 same condition and manner as Example 1.

#### Example 13

A percutaneous absorption preparation of the present  
invention was prepared in the same manner as Example 1 in  
such a composition that in place of Compound A in Example  
10 12, the same amount of (S)-N-[2-(1,6,7,8-tetrahydro-2H-  
indeno[5,4-b]furan-8-yl)ethyl]acetamide obtained in  
Reference example 1 is blended.

#### Reference example 1

(S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-  
15 yl)ethyl]acetamide

To a solution of (S)-2-[1,6,7,8-tetrahydro-2H-  
indeno[5,4-b]furan-8-yl]ethylamine hydrochloride (71.92 g,  
0.3 mol) in dichloromethane (500 mL), triethylamine (104.6  
mL, 0.75 mol), dimethylaminopyridine (3.67 g, 0.03 mol) and  
20 acetic anhydride (31.2 mL, 0.33 mol) were added under ice-  
cooling, and stirred four 16 hour at room temperature. The  
reaction mixture was poured into cold water and the organic  
layer was separated. The organic layer was washed with 1N  
hydrochloric acid and saturated brine and dried over sodium  
25 sulfate, followed by purification by a small amount of



silica gel chromatography (dichloromethane). After  
distilling off the solvent under reduced pressure, the  
obtained crystal was recrystallized from isopropyl  
ether/ethyl acetate to give the title compound (yield: 53.2  
5 g, 72%).

Melting point: 118-120°C

NMR(CDCl<sub>3</sub>)  $\delta$ : 1.50-1.92 (2H, m), 1.96 (3H, s), 1.96-  
2.13 (1H, m), 2.19-2.38 (1H, m), 2.67-2.95 (2H, m), 3.00-  
3.9 (5H, m), 4.43-4.64 (2H, m), 5.43 (1H, br), 6.62 (1H, d, J=7.8 Hz),  
10 6.95 (1H, d, J=7.8 Hz).

Elemental Analysis for C<sub>15</sub>H<sub>19</sub>NO<sub>2</sub>

Calcd: C, 73.44, H, 7.81, N, 5.71

Found: C, 73.56, H, 7.89, N, 5.86

Angle of rotation:  $[\alpha]_D = -59.1^\circ$  (c=1.0%, chloroform)

15 Test example 1

Male SD rats in 7 weeks-old (body weight about 250 g,  
3 or 4 per one administration group) were anaesthetized by  
ether, and after shaving the body hair of abdomen,  
percutaneous absorption preparations according to Examples  
20 1 and 2 which are cut into pieces so that the affix area  
becomes 30 cm<sup>2</sup> or 7.1 cm<sup>2</sup> were affixed, and the pieces were  
wounded and fixed by stretchable bandage from above so that  
the plaster will not come off. The contents of Compound A  
in the administered percutaneous absorption preparations  
25 were calculated to be 27 mg and 9 mg per 30 cm<sup>2</sup>,

respectively.

After affixing, the rats were placed back to the respective cages under no anesthesia, and blood samples were collected at regular interval from tail veins, and the blood concentrations of the Compound A were quantified by means of the HPLC.

1) Extraction of drug from plasma

0.1 mL of plasma was taken in a 10 mL test tube, to which 0.5 mL of 0.05 M phosphoric buffer (pH7) and 5 mL of diethylether were added. After shaking for 15 minutes, the drug was extracted by ether, and 4.5 mL of the ether solution was evaporated and dried to be solidified and then dissolved by adding an HPLC eluate to give an HPLC quantification sample.

2) HPLC condition

Column: TSKgel ODS-80Ts QA (4.6 mmI.D., 150 mm, Tosoh)

Eluate 1: 0.01 M  $\text{CH}_3\text{COONH}_4/\text{CH}_3\text{CN}$  (ratio in volume 60:40)

Eluate 2: 0.01 M  $\text{CH}_3\text{COONH}_4/\text{CH}_3\text{CN}$  (ratio in volume 10:90)

Flow rate: 1 mL/min

Gradient program:

Time (min)	0	7	12	15	15.1
Eluate 1	100%	100%	0%	0%	100%
Eluate 2	0%	0%	100%	100%	0%

Column temperature: 40°C

Detection: at UV 210 nm

Maximum concentration of Compound A in plasma after affixing each administration (Cmax) and its reach time (Tmax) and bioavailability (BA) of the same formulation for intravenous administration will be shown in Table 5.

[Table 5]

Administered sample	Affix area	Cmax	Tmax	BA
Percutaneous absorption	30 cm <sup>2</sup>	2200 ng/mL	8 hours	61%
preparation of Example 1	7.1 cm <sup>2</sup>	250 ng/mL	8 hours	40%
Percutaneous absorption	30 cm <sup>2</sup>	580 ng/mL	6 hours	52%
preparation of Example 2	7.1 cm <sup>2</sup>	200 ng/mL	6 hours	52%

In the percutaneous absorption preparations of Examples 1 and 2, one peak of blood-drug-concentration-time profile that reaches the maximum blood concentration 6 to 8 hours after affixing was observed, and it was found that the amount of absorption relies upon loading amount and affixing area. In addition, no administration groups show any abnormality in the post-experimental observation of the skin part where the agent had been affixed conducted.

Test example 2

The percutaneous absorption preparation of Example 3 was administered to rats by affixing the preparation on

their abdomens in the same manner as Test example 1 and blood concentration of Compound A after administration was measured in the same manner as Test example 1. Average plasma level during 0 to 24 hours was about 50 ng/mL and BA was about 12%.

#### Test example 3

The percutaneous absorption preparation of Example 4 was administered to rats by affixing the preparation on their abdomen in the same manner as Test example 1 and blood concentration of Compound A after administration was measured in the same manner as Test example 1. As for Prescriptions A and B, average plasma concentration during 0 to 24 hours was about 50 ng/mL and BA of each prescription was 15% and 20%, respectively. Prescription C showed C<sub>max</sub> 210 ng/mL at 8 hours, and BA of 30%.

#### Comparative example

A composition in which a self-crosslinking acrylic copolymer which is an adhesive agent and Compound A which is an active ingredient were blended in a proportion of 98:2 (w/w) was prepared, and a comparative percutaneous absorption preparation was obtained in the same condition and manner as Example 1. The obtained agent was administered to rats by affixing the agent on their abdomens in the same manner as Test example 1 and blood concentration of Compound A after administration was

measured in the same manner as Test example 1. Average plasma level during 0 to 24 hours was not more than 10 ng/mL, and a blood-drug-concentration-time profile not having a clear Cmax was observed, and BA was about 2%.

5           From the above, it can be concluded that the percutaneous absorption preparations of the present invention enable the active ingredient to be absorbed into the body through a skin contact surface by a convenient administration system, providing a favorable blood-drug-  
10           concentration-time profile in which the blood concentration of the active ingredient is kept for 6 to 12 hours.

#### Industrial Applicability

15           The percutaneous absorption preparations of the present invention enable a compound having a melatonin receptor agonist activity to be absorbed by a convenient administration system, present favorable blood-drug-concentration-time profile in which blood concentration of the active ingredient is kept for 6 to 12 hours in contrast  
20           to the case of oral administration, and can exert an therapeutic effect on a disease caused by a decrease in melatonin secretion at night.